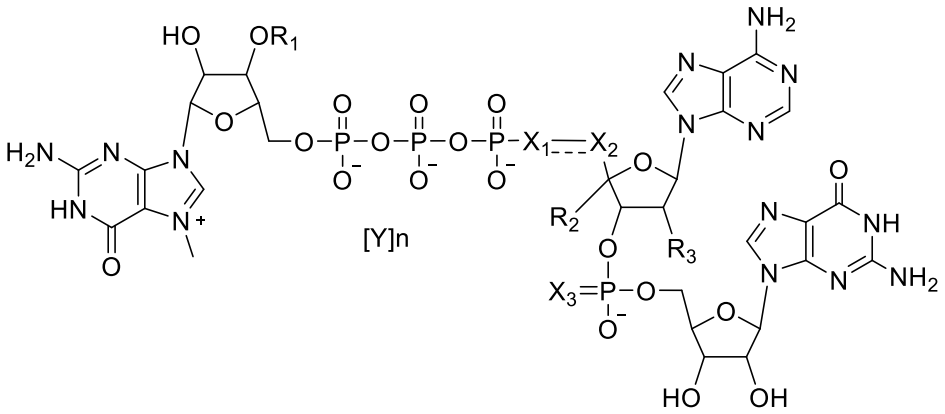
WHAT IS CLAIMED IS:

1. A compound of the following formula:



Formula I

or a stereoisomer thereof, wherein:

$\equiv$ is a single bond or a double bond;

R_1 is H or CH_3;

R_2 is H and R_3 is OCH_3 or F, or R_2 and R_3 are covalently bonded together and, together with intermediate atoms, form a 2'-O, 4'-C methylene bridge;

X_1 is O or CH;

X_2 is CH_2 or CH;

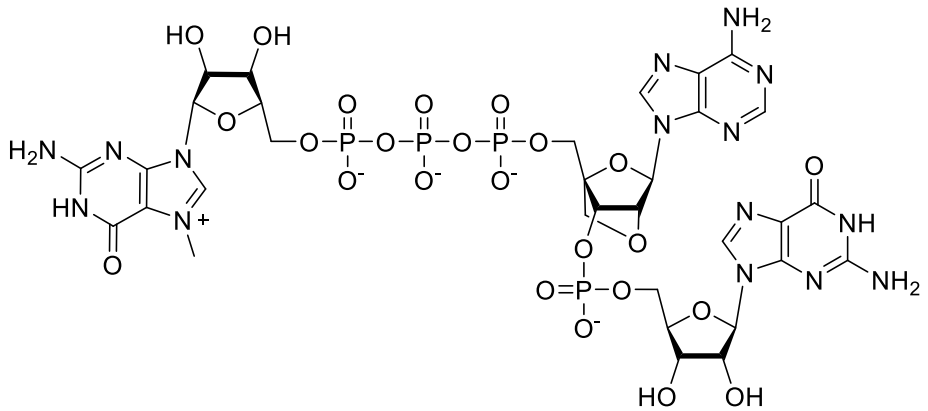
X_3 is O or S;

each independent Y is H^+ or a cation; and

n is 0, 1, 2, 3, or 4,

wherein when X_1 is CH, X_2 is CH and $\equiv$ is a double bond.

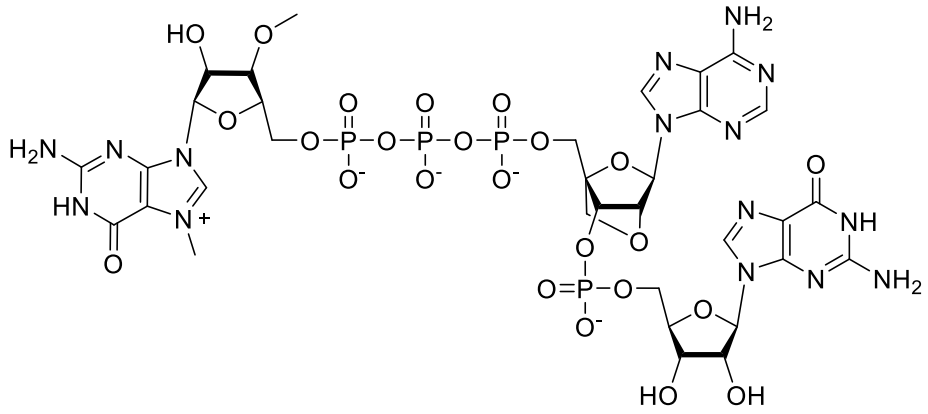
2. The compound of claim 1, wherein the compound has the following structure:



Compound 1

or a stereoisomer thereof.

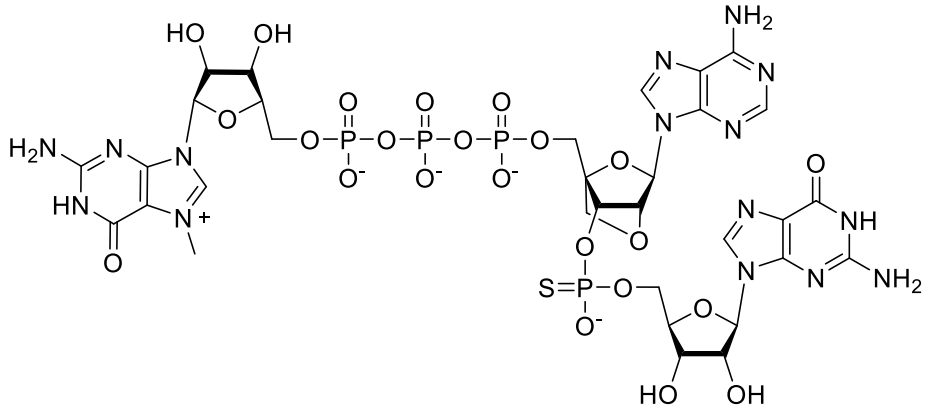
3. The compound of claim 1, wherein the compound has the following structure:



Compound 2

or a stereoisomer thereof.

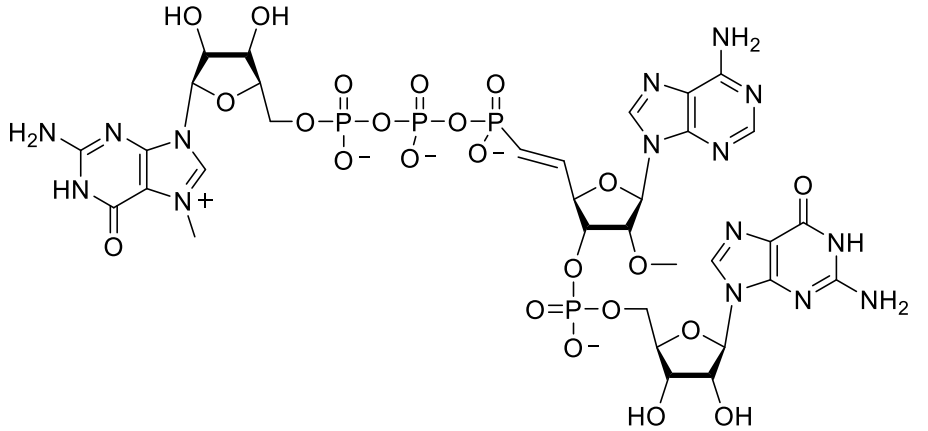
4. The compound of claim 1, wherein the compound has the following structure:



Compound 3

or a stereoisomer thereof.

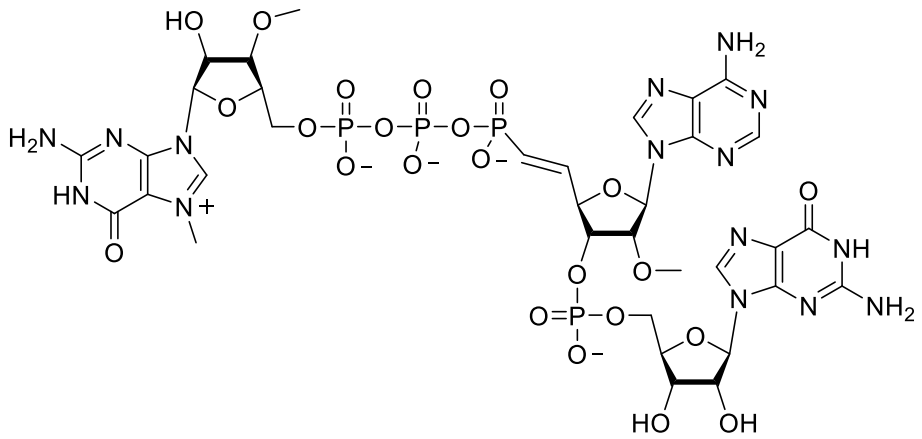
5. The compound of claim 1, wherein the compound has the following structure:



Compound 4

or a stereoisomer thereof.

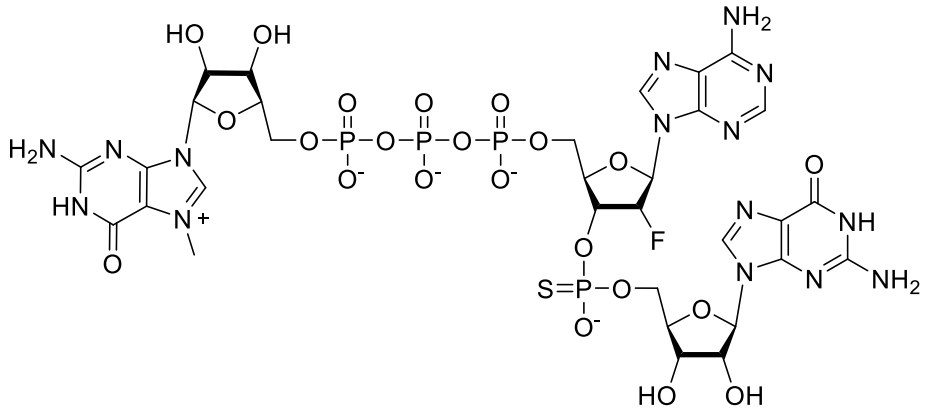
6. The compound of claim 1, wherein the compound has the following structure:



Compound 5

or a stereoisomer thereof.

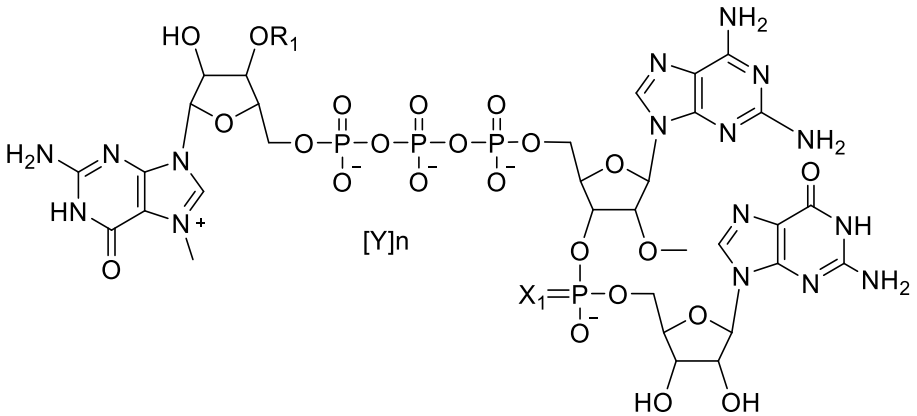
7. The compound of claim 1, wherein the compound has the following structure:



Compound 6

or a stereoisomer thereof.

8. A compound of the following formula:



Formula II

or a stereoisomer thereof, wherein:

R_1 is H or CH_3;

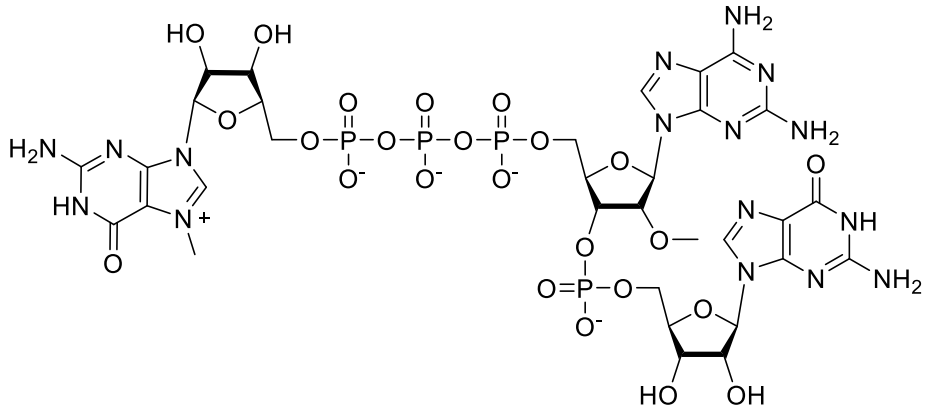
X_1 is O or S;

each independent Y is H^+ or a cation; and

n is 0, 1, 2, 3, or 4,

wherein when X_1 is S, R_1 is CH_3.

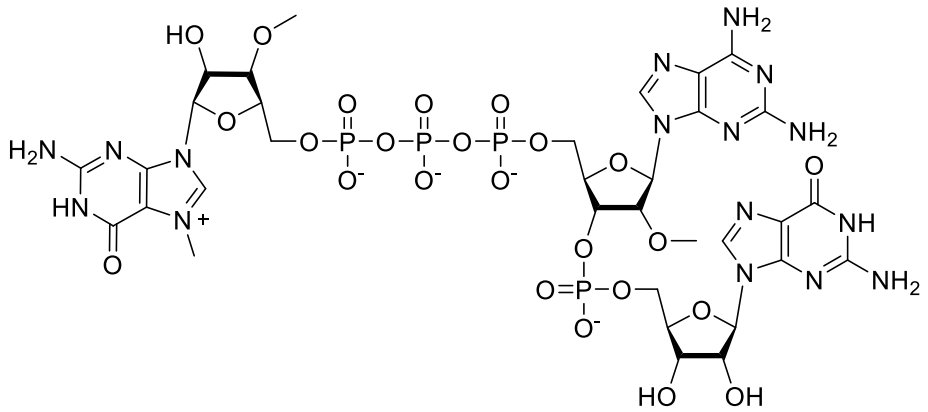
9. The compound of claim 8, wherein the compound has the following structure:



Compound 7

or a stereoisomer thereof.

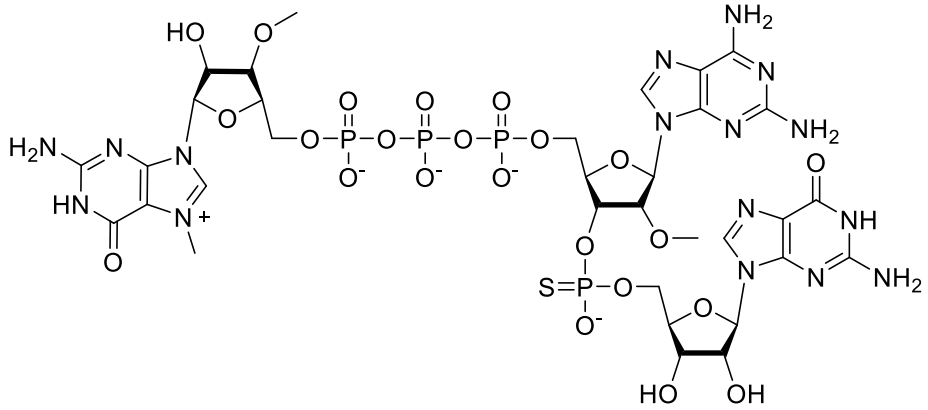
10. The compound of claim 8, wherein the compound has the following structure:



Compound 8

or a stereoisomer thereof.

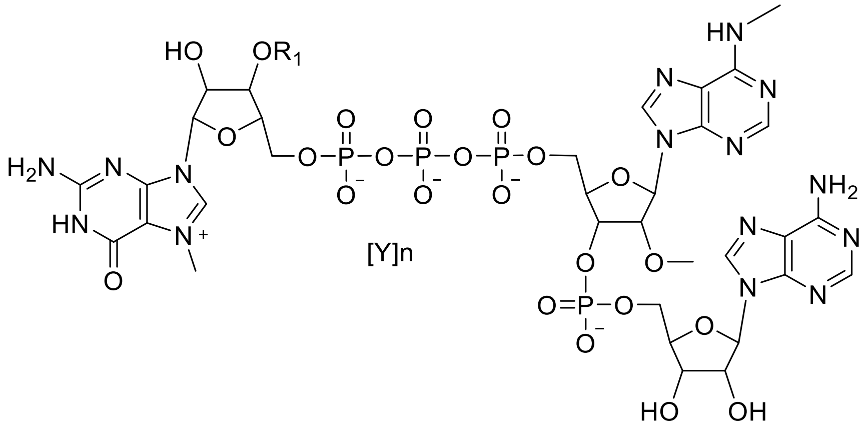
11. The compound of claim 8, wherein the compound has the following structure:



Compound 9

or a stereoisomer thereof.

12. A compound of the following formula:



Formula III

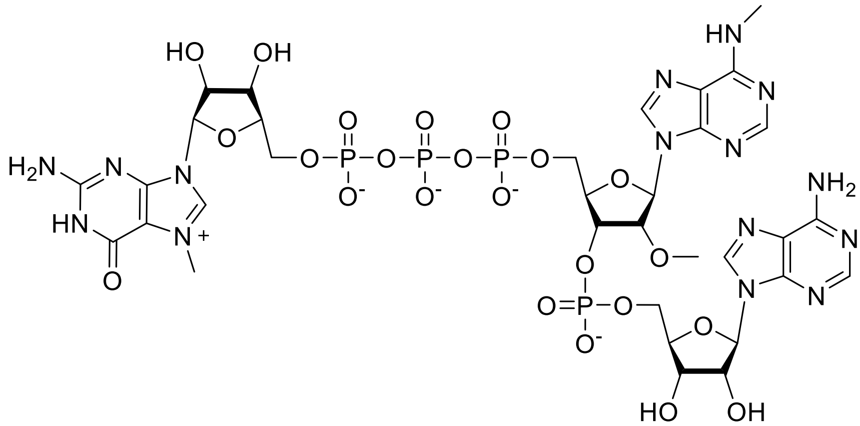
or a stereoisomer thereof, wherein:

R_1 is H or CH_3;

each independent Y is H^+ or a cation; and

n is 0, 1, 2, 3, or 4.

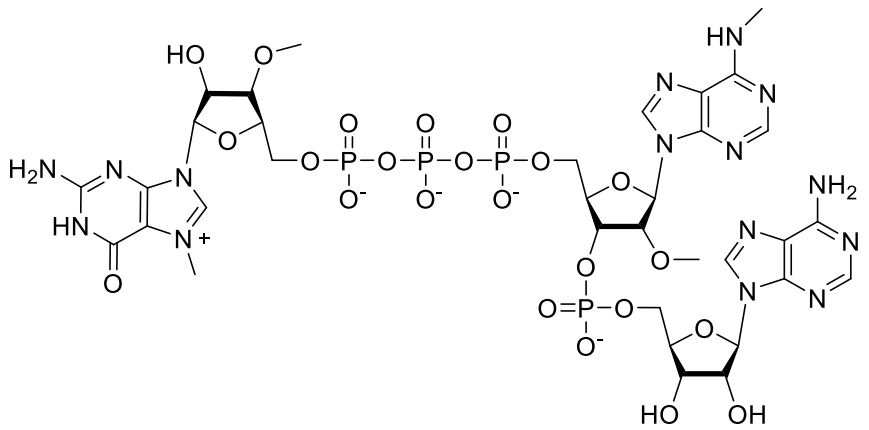
13. The compound of claim 12, wherein the compound has the following structure:



Compound 10

or a stereoisomer thereof.

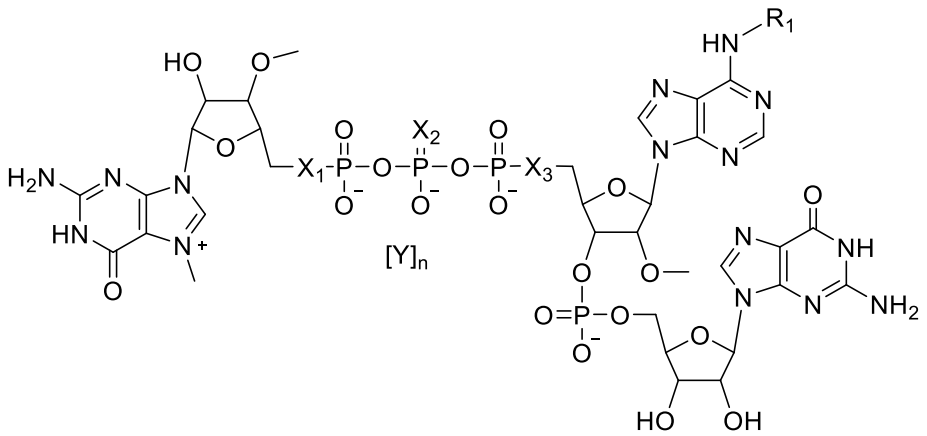
14. The compound of claim 12, wherein the compound has the following structure:



Compound 11

or a stereoisomer thereof.

15. A compound of the following formula:



Formula IV

or a stereoisomer thereof, wherein:

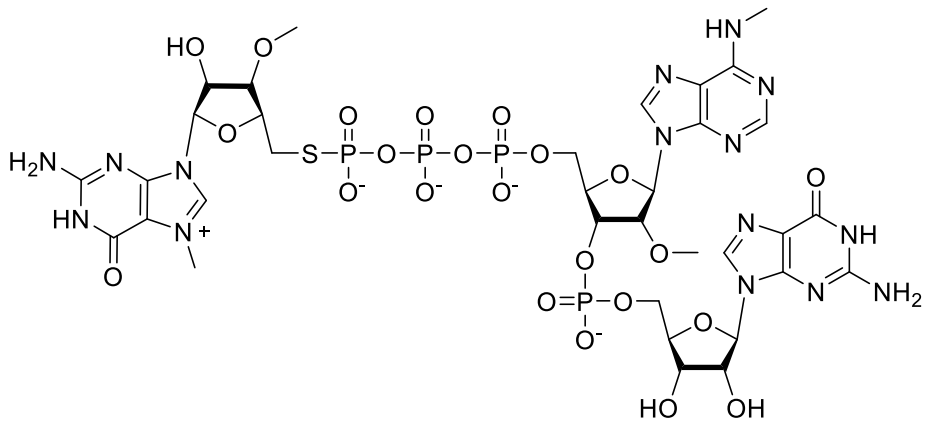
R_1 is H or CH_3;

X_1, X_2, and X_3 are each independently selected from O and S, wherein when one of X_1, X_2, or X_3 is S, the remaining of X_1, X_2, and X_3 are O;

each independent Y is H^+ or a cation; and

n is 0, 1, 2, 3, or 4.

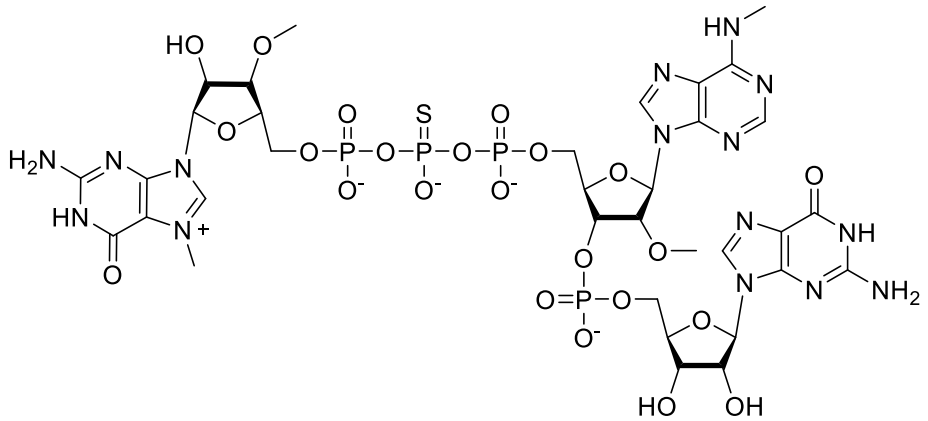
16. The compound of claim 15, wherein the compound has the following structure:



Compound 12

or a stereoisomer thereof.

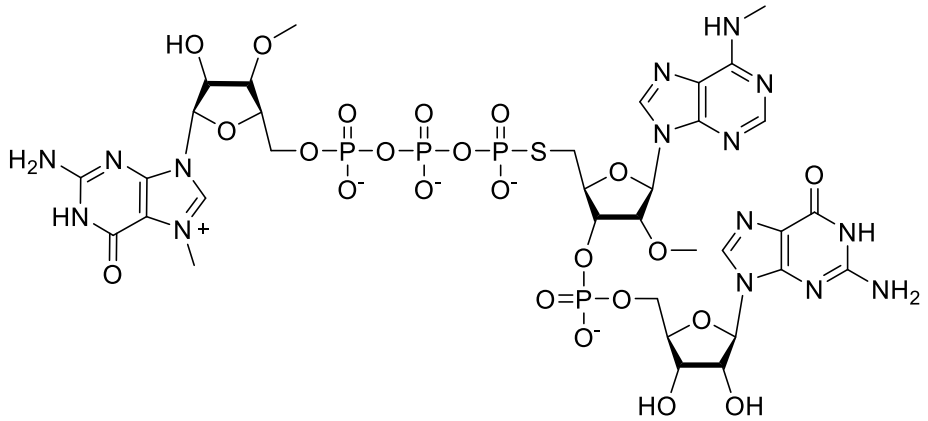
17. The compound of claim 15, wherein the compound has the following structure:



Compound 13

or a stereoisomer thereof.

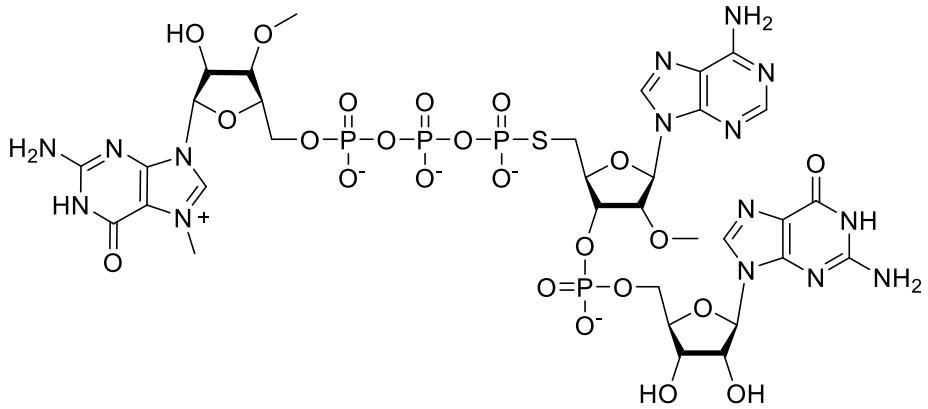
18. The compound of claim 15, wherein the compound has the following structure:



Compound 14

or a stereoisomer thereof.

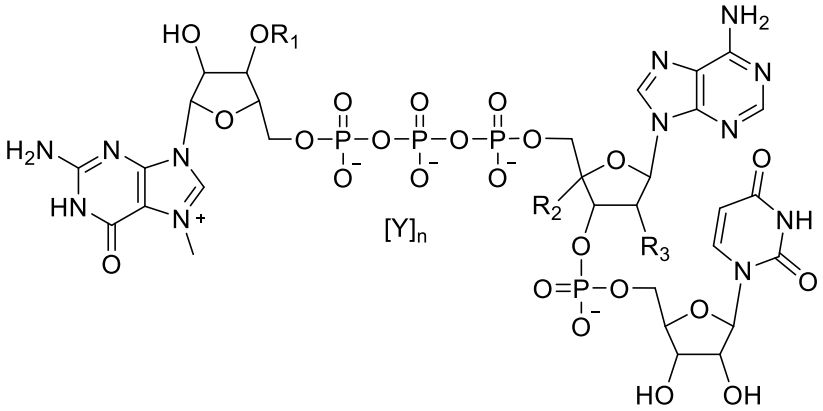
19. The compound of claim 15, wherein the compound has the following structure:



Compound 73

or a stereoisomer thereof.

20. A compound of the following formula:



Formula V

or a stereoisomer thereof, wherein:

R_1 is H or CH_3;

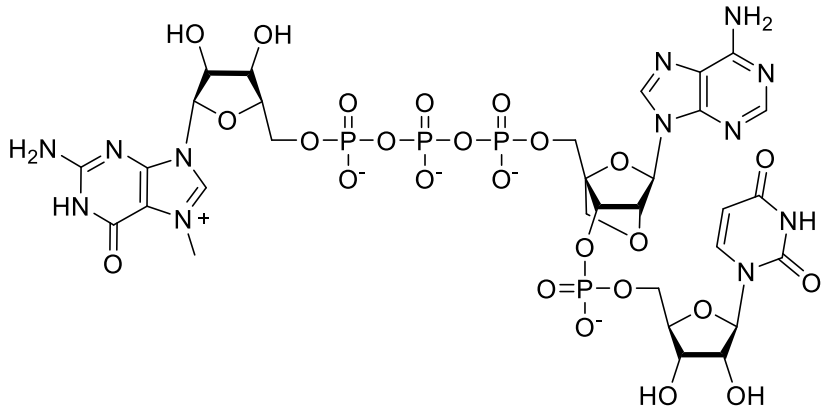
R_2 is H and R_3 is F, or R_2 and R_3 are covalently bonded together and, together with intermediate atoms, form a 2'-O, 4'-C methylene bridge;

each independent Y is H^+ or a cation; and

n is 0, 1, 2, 3, or 4,

wherein when R_2 is H and R_3 is F, R_1 is not H.

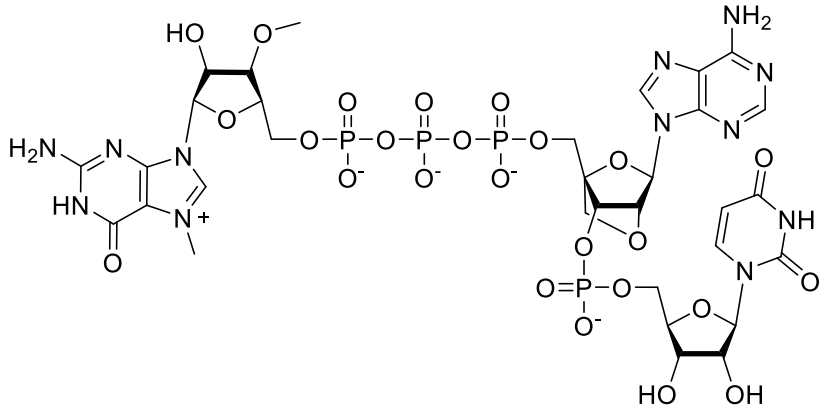
21. The compound of claim 20, wherein the compound has the following structure:



Compound 15

or a stereoisomer thereof.

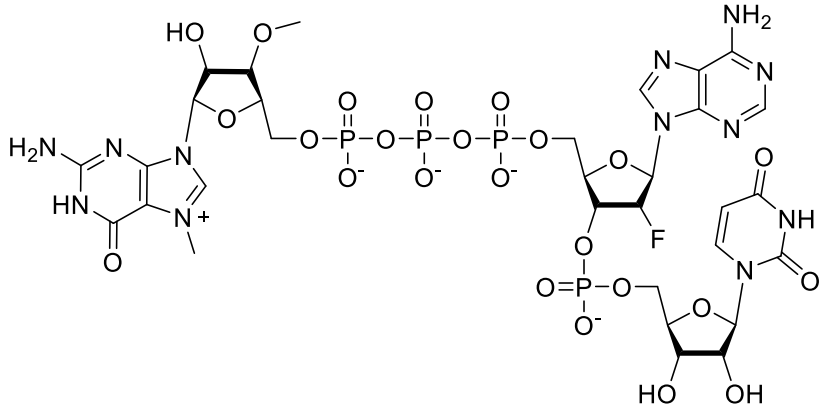
22. The compound of claim 20, wherein the compound has the following structure:



Compound 16

or a stereoisomer thereof.

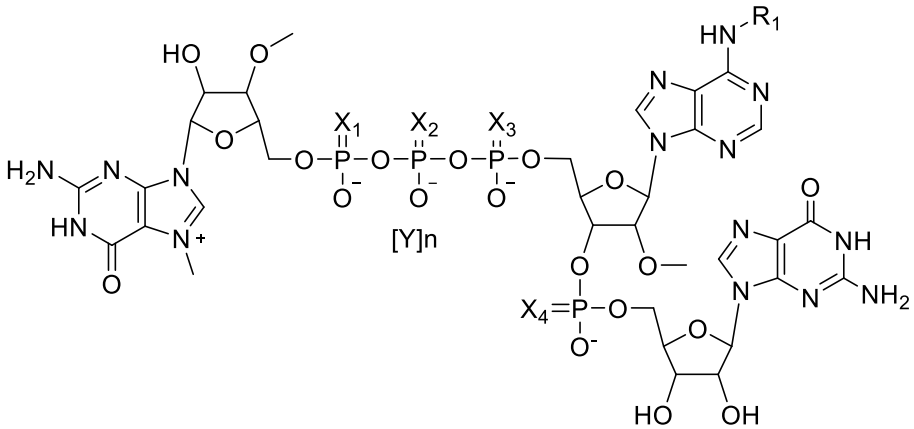
23. The compound of claim 20, wherein the compound has the following structure:



Compound 17

or a stereoisomer thereof.

24. A compound of the following formula:



Formula VI

or a stereoisomer thereof, wherein:

R_1 is H or CH_3;

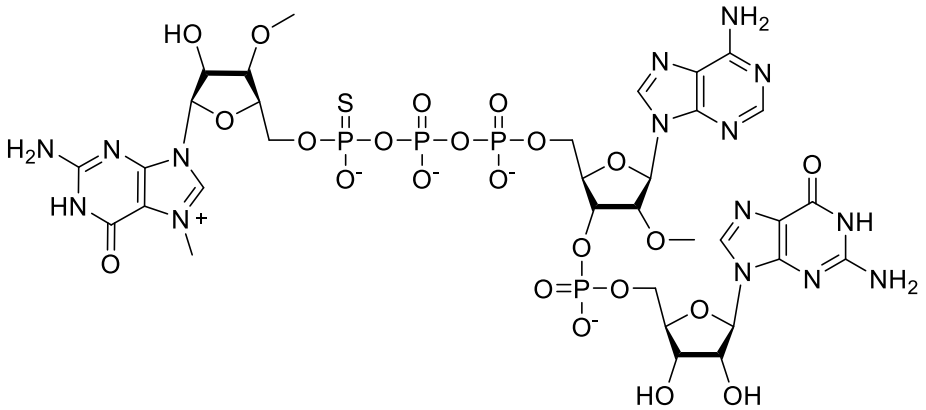
X_1, X_2, X_3, and X_4 are each independently selected from O and S;

each independent Y is H^+ or a cation; and

n is 0, 1, 2, 3, or 4,

wherein one of X_1, X_2, X_3, and X_4 is S.

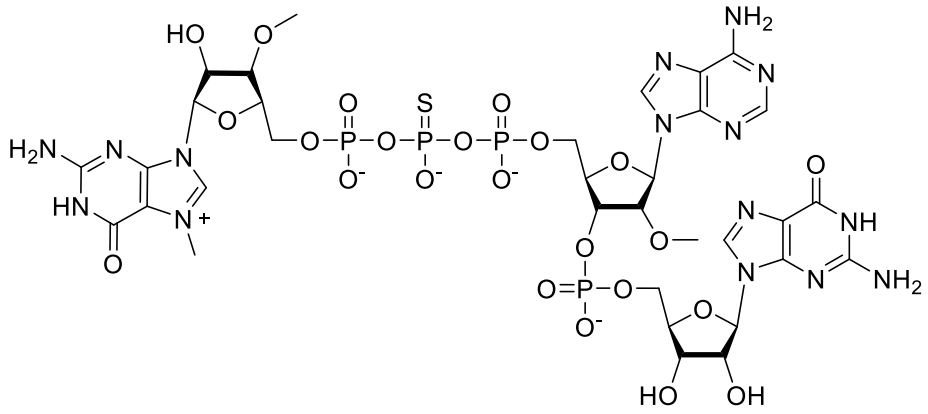
25. The compound of claim 24, wherein the compound has the following structure:



Compound 18

or a stereoisomer thereof.

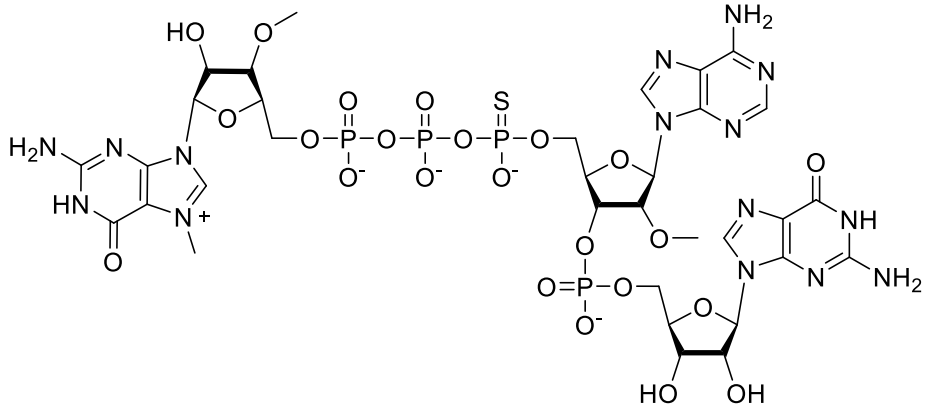
26. The compound of claim 24, wherein the compound has the following structure:



Compound 19

or a stereoisomer thereof.

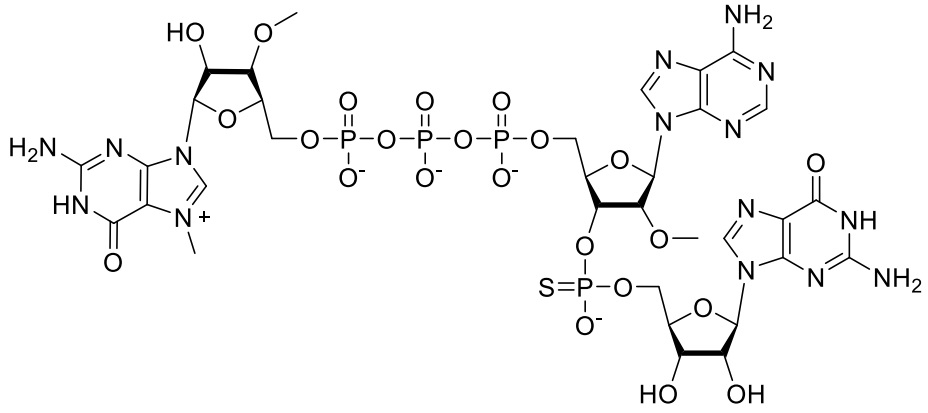
27. The compound of claim 24, wherein the compound has the following structure:



Compound 20

or a stereoisomer thereof.

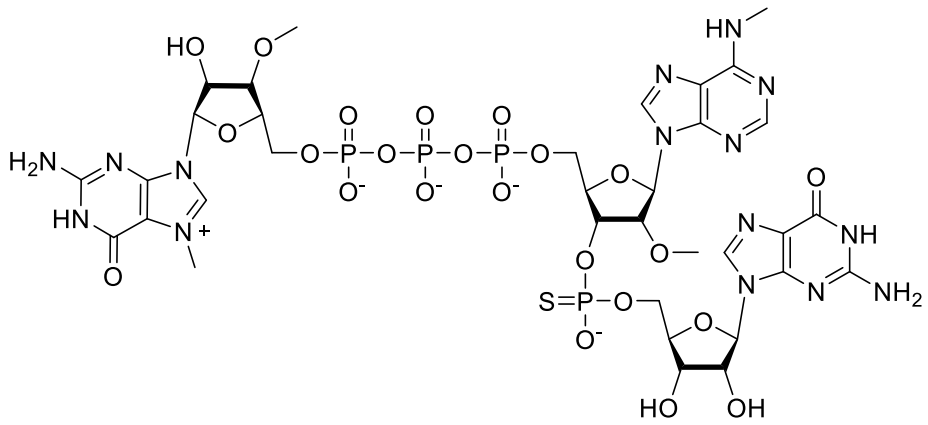
28. The compound of claim 24, wherein the compound has the following structure:



Compound 21

or a stereoisomer thereof.

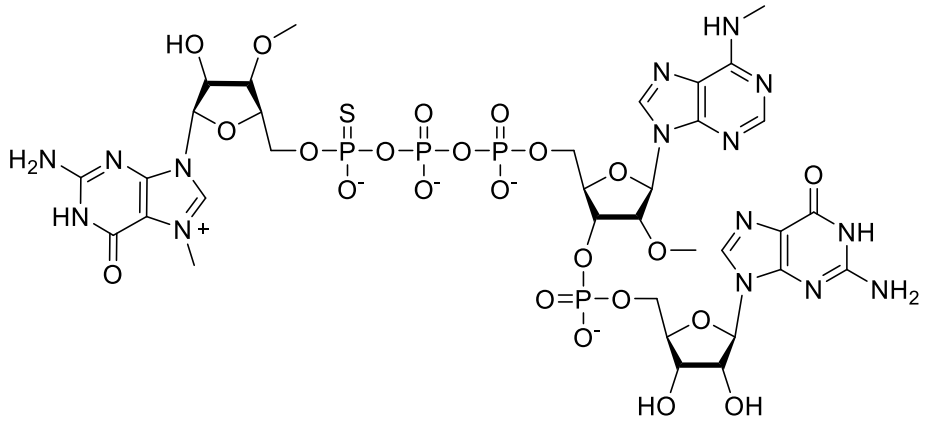
29. The compound of claim 24, wherein the compound has the following structure:



Compound 74

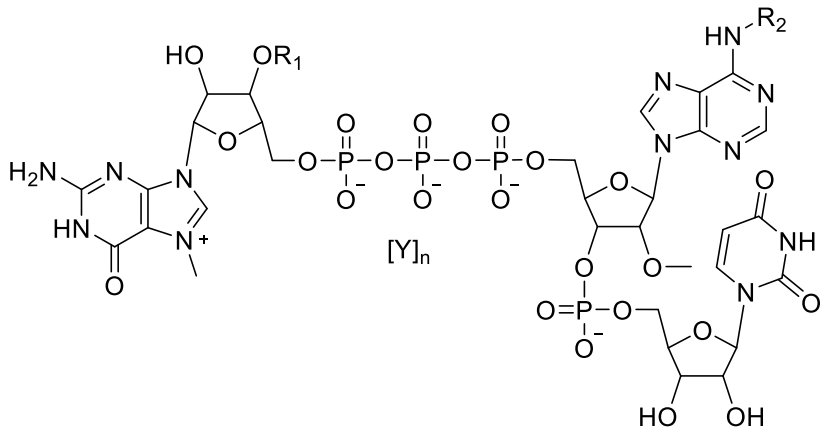
or a stereoisomer thereof.

30. The compound of claim 24, wherein the compound has the following structure:



Compound 81

31. A compound of the following formula:



Formula VII

or a stereoisomer thereof, wherein:

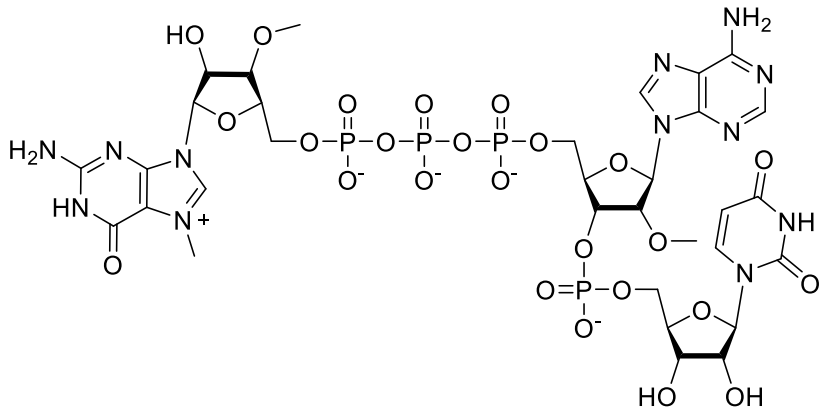
R_1 and R_2 are each independently selected from H and CH_3;

each independent Y is H^+ or a cation; and

n is 0, 1, 2, 3, or 4,

wherein at least one of R_1 or R_2 is CH_3.

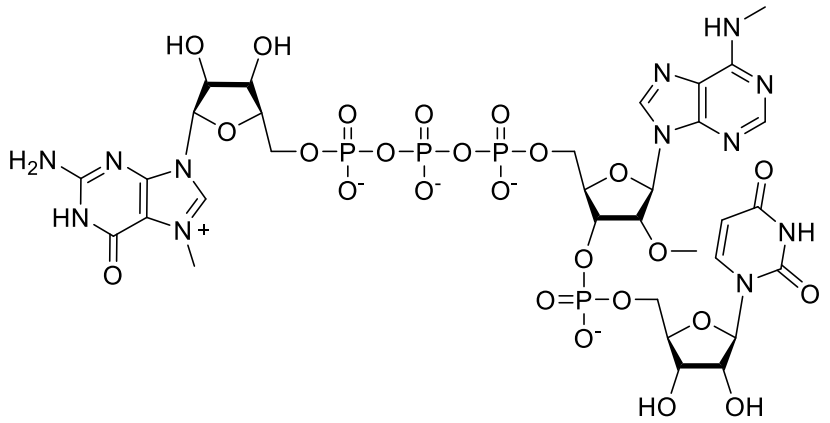
32. The compound of claim 31, wherein the compound has the following structure:



Compound 22

or a stereoisomer thereof.

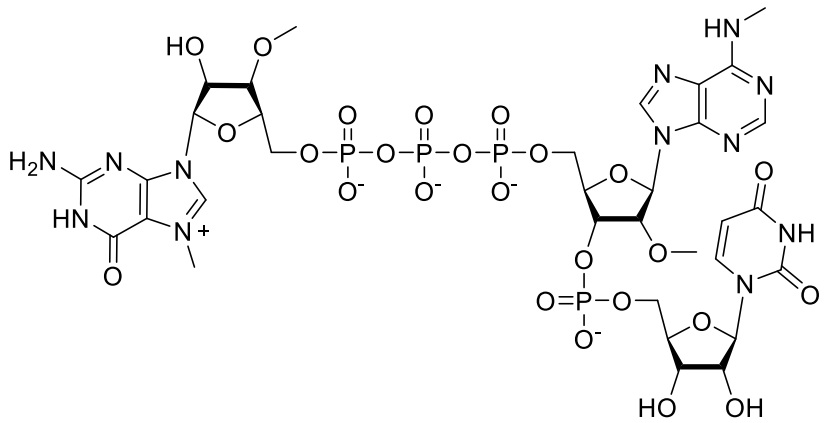
33. The compound of claim 31, wherein the compound has the following structure:



Compound 23

or a stereoisomer thereof.

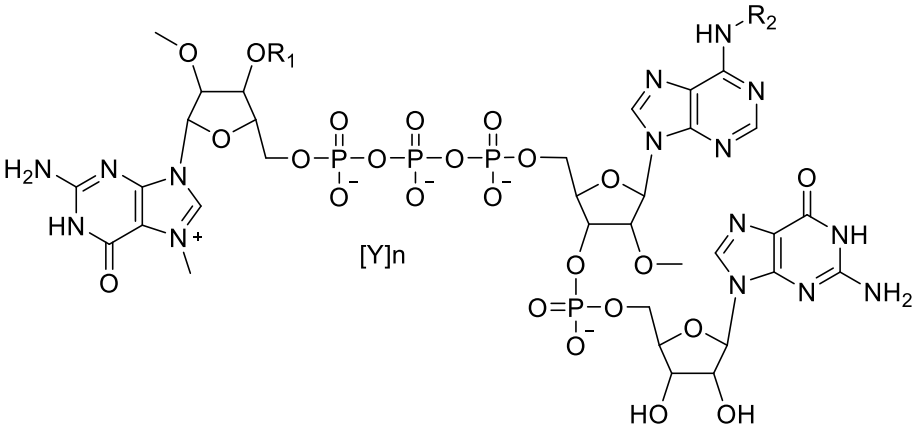
34. The compound of claim 31, wherein the compound has the following structure:



Compound 24

or a stereoisomer thereof.

35. A compound of the following formula:



Formula VIII

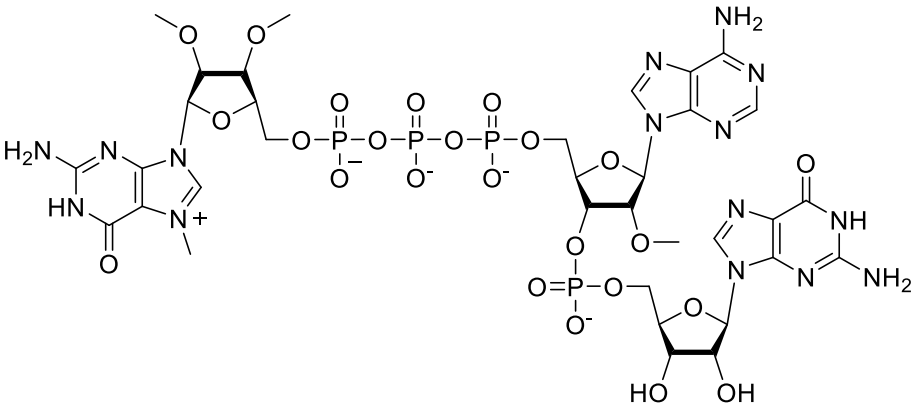
or a stereoisomer thereof, wherein:

R_1 and R_2 are each independently selected from H and CH_3;

each independent Y is H^+ or a cation; and

n is 0, 1, 2, 3, or 4.

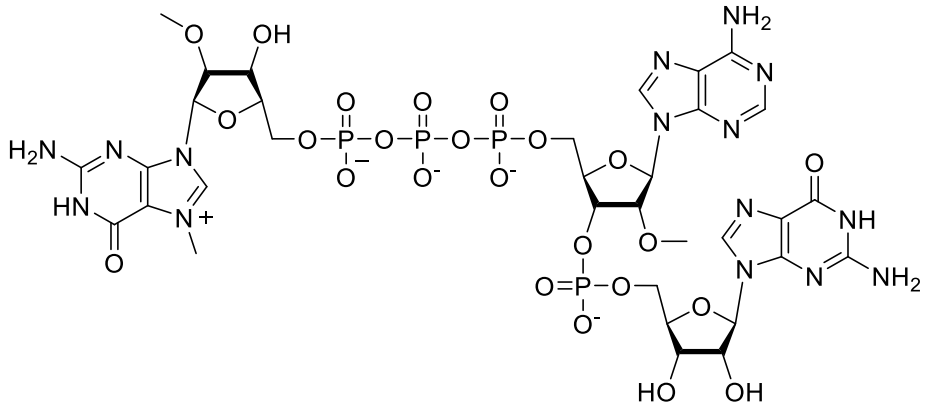
36. The compound of claim 35, wherein the compound has the following structure:



Compound 25

or a stereoisomer thereof.

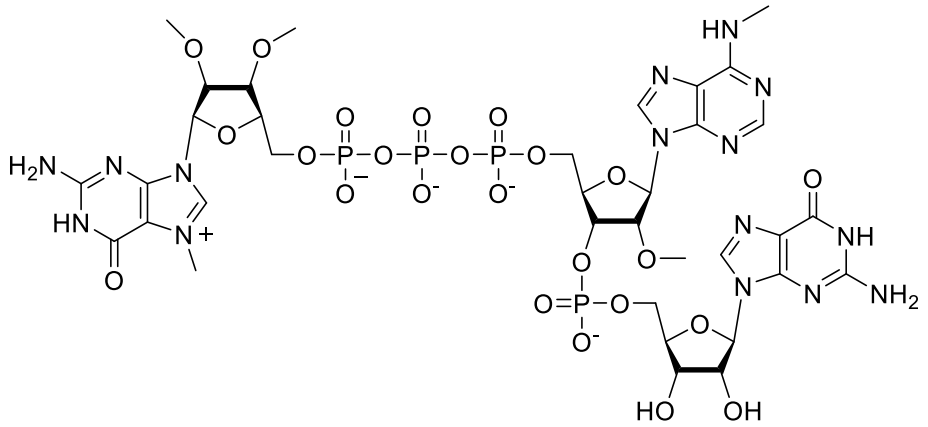
37. The compound of claim 35, wherein the compound has the following structure:



Compound 26

or a stereoisomer thereof.

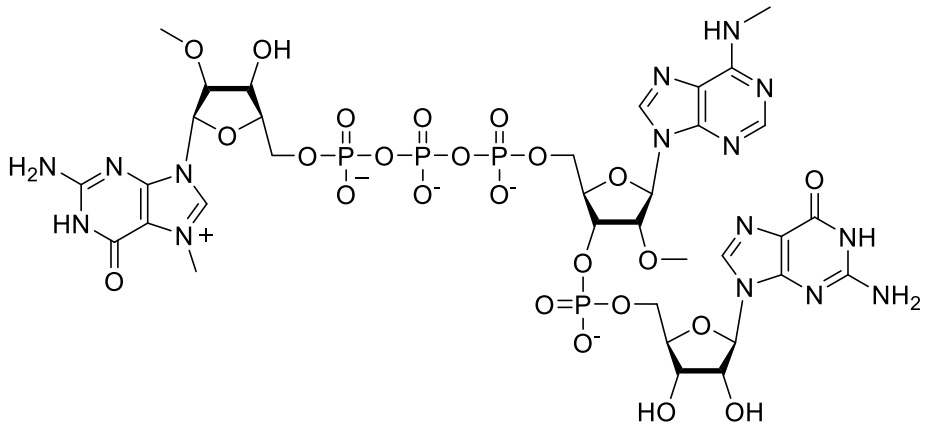
38. The compound of claim 35, wherein the compound has the following structure:



Compound 27

or a stereoisomer thereof.

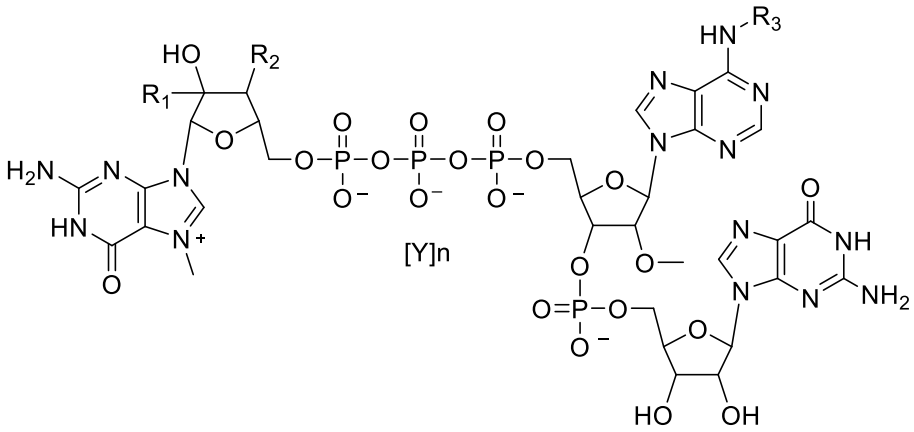
39. The compound of claim 35, wherein the compound has the following structure:



Compound 28

or a stereoisomer thereof.

40. A compound of the following formula:



Formula IX

or a stereoisomer thereof, wherein:

R_1 is H or CH_3;

R_2 is OH, F, substituted or unsubstituted alkoxy, or thio;

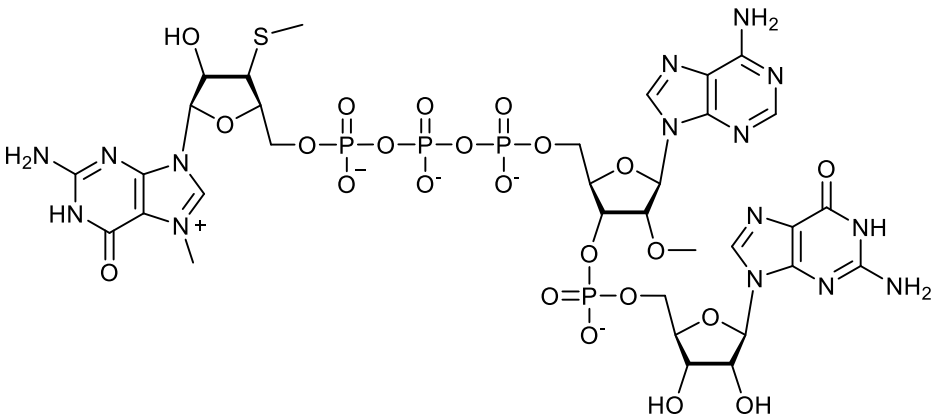
R_3 is H or CH_3;

each independent Y is H^+ or a cation;

and n is 0, 1, 2, 3, or 4,

wherein when R_2 is OH, R_1 is not H.

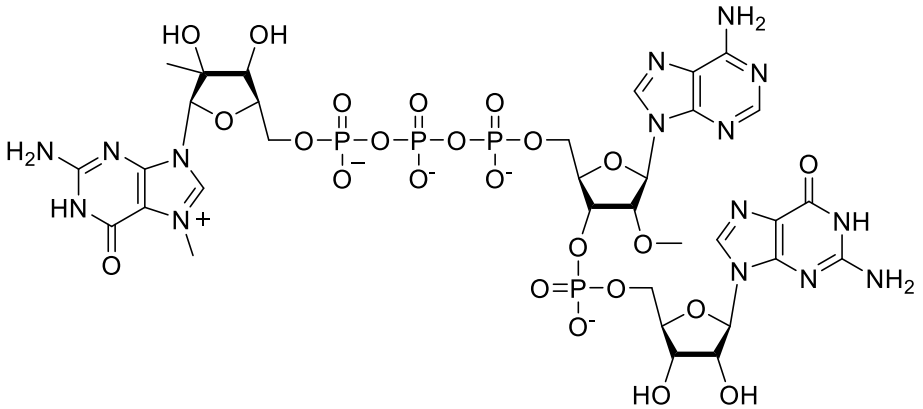
41. The compound of claim 40, wherein the compound has the following structure:



Compound 42

or a stereoisomer thereof.

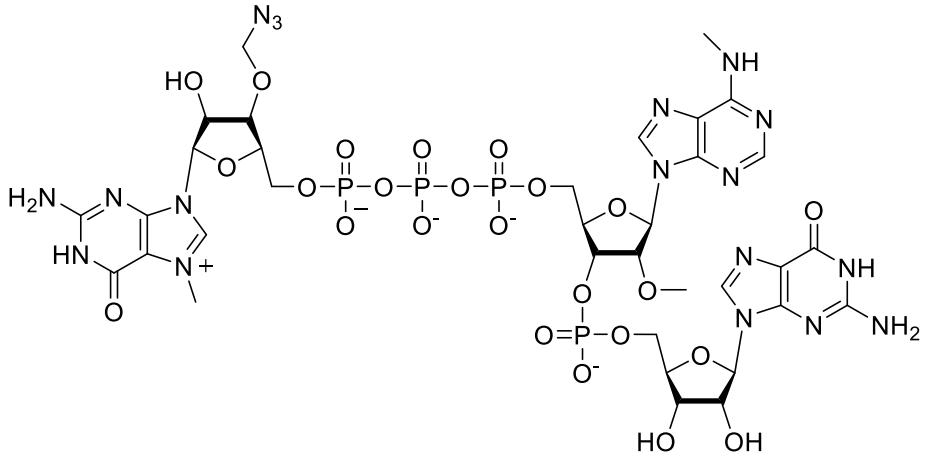
42. The compound of claim 40, wherein the compound has the following structure:



Compound 43

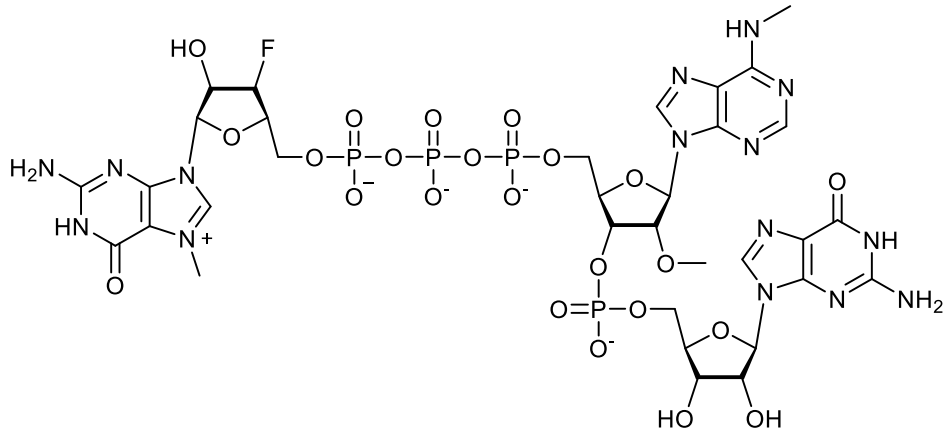
or a stereoisomer thereof.

43. The compound of claim 40, wherein the compound has the following structure:



Compound 45

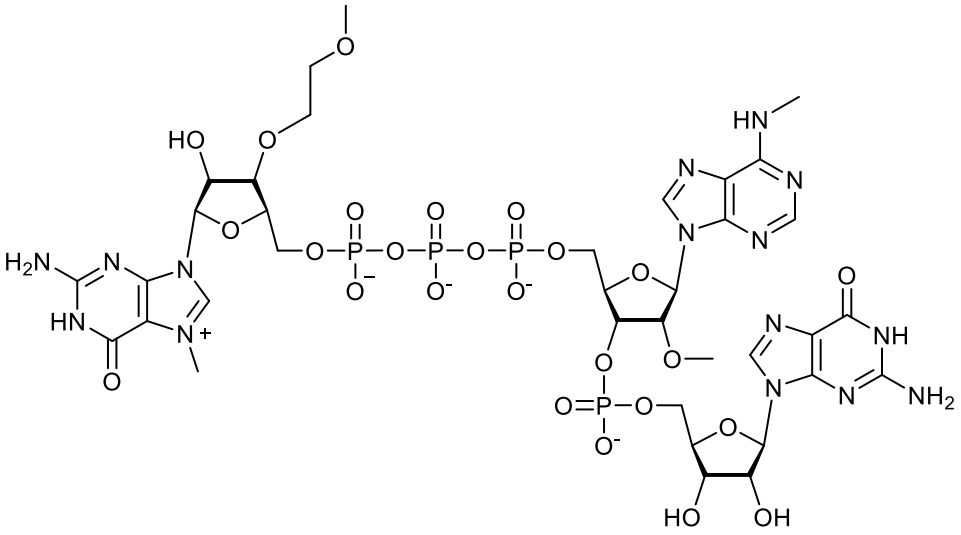
44. The compound of claim 40, wherein the compound has the following structure:



Compound 49

or a stereoisomer thereof.

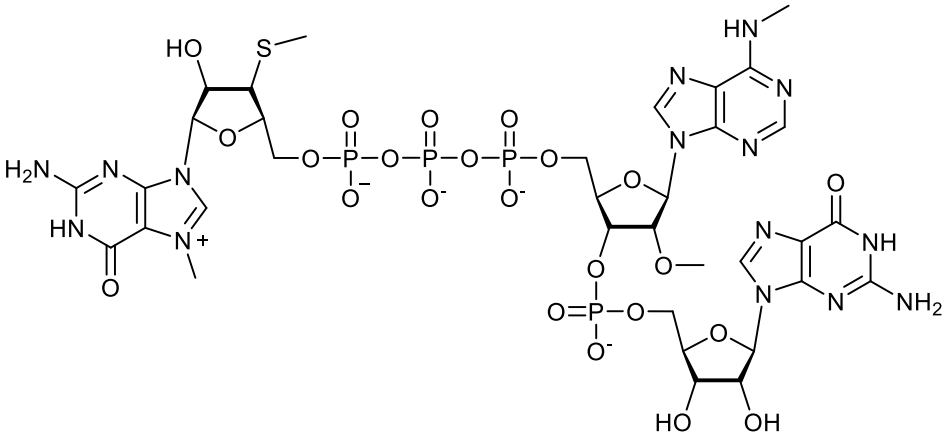
45. The compound of claim 40, wherein the compound has the following structure:



Compound 50

or a stereoisomer thereof.

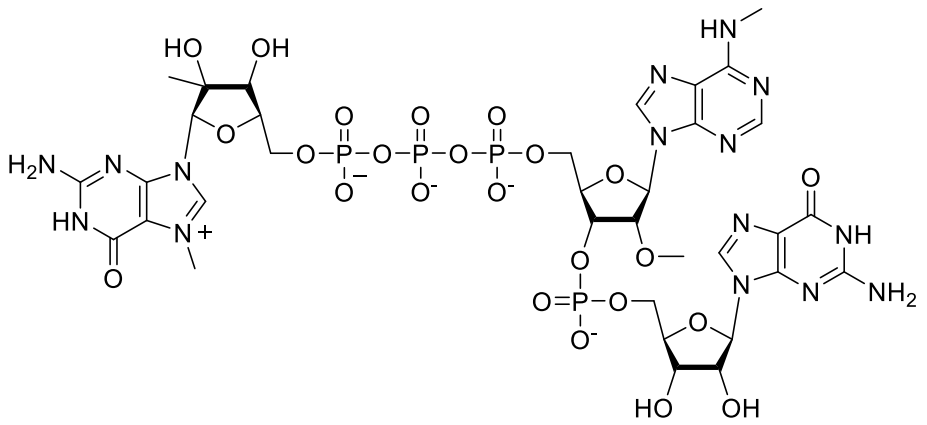
46. The compound of claim 40, wherein the compound has the following structure:



Compound 52

or a stereoisomer thereof.

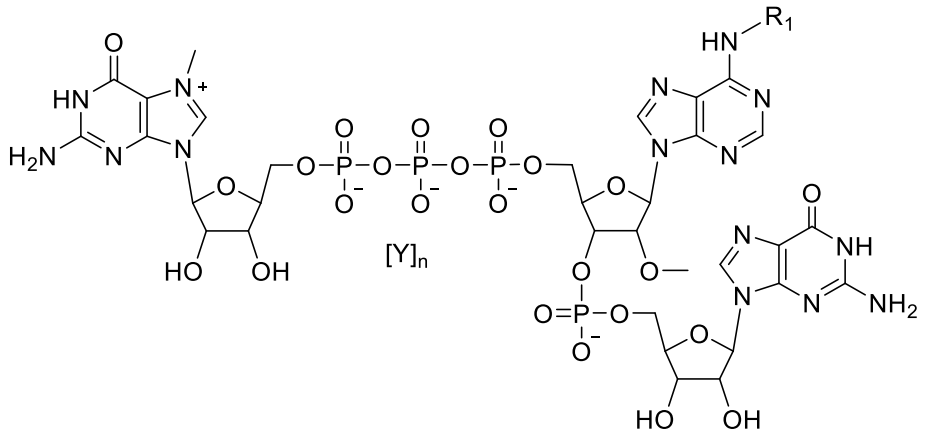
47. The compound of claim 40, wherein the compound has the following structure:



Compound 76

or a stereoisomer thereof.

48. A compound of the following formula:



Formula X

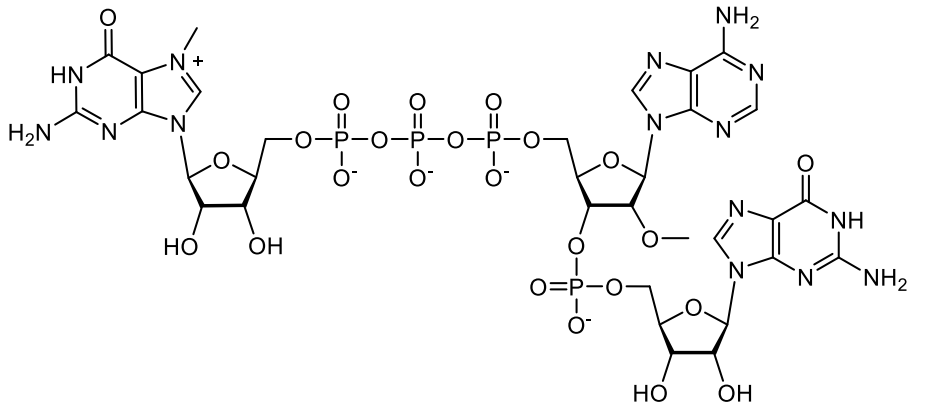
or a stereoisomer thereof, wherein:

R_1 is H and CH_3;

each independent Y is H^+ or a cation; and

n is 0, 1, 2, 3, or 4.

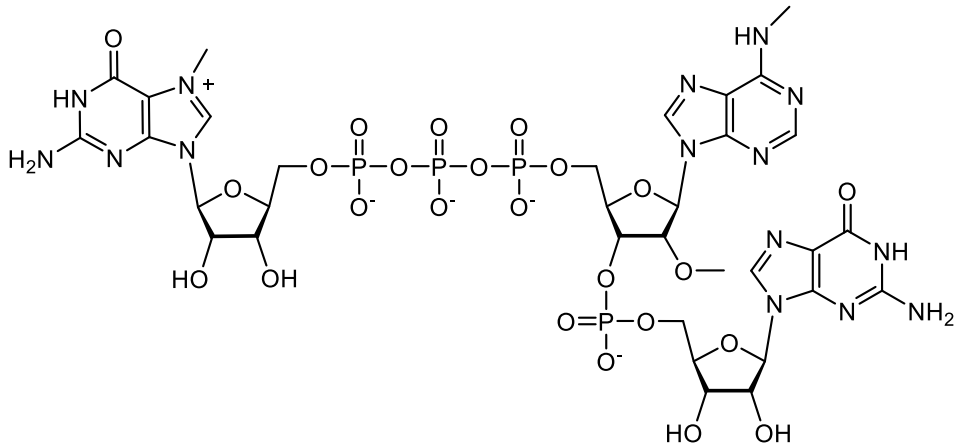
49. The compound of claim 48, wherein the compound has the following structure:



Compound 75

or a stereoisomer thereof.

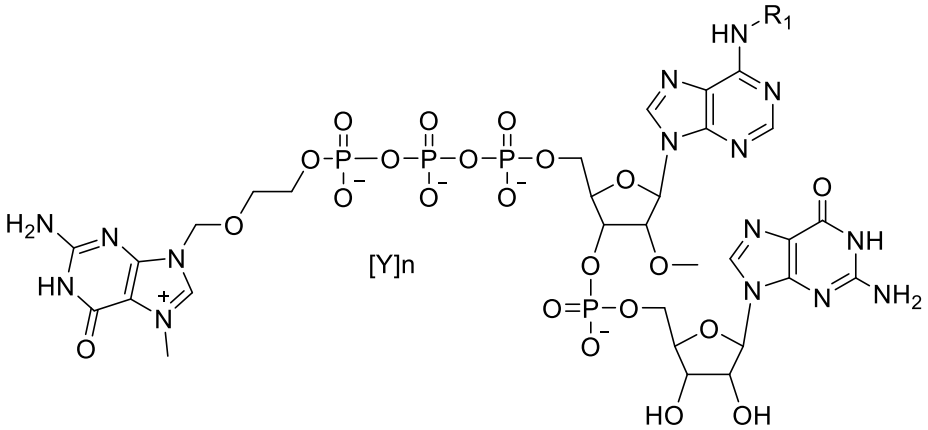
50. The compound of claim 48, wherein the compound has the following structure:



Compound 77

or a stereoisomer thereof.

51. A compound of the following formula:



Formula XI

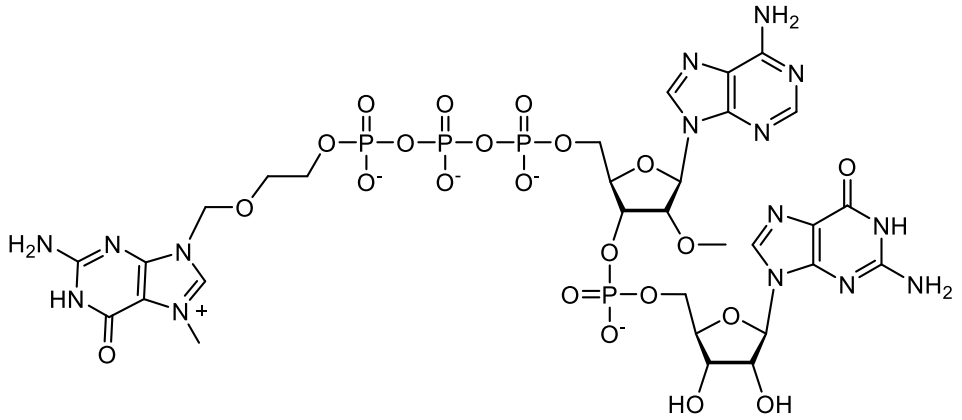
or a stereoisomer thereof, wherein:

R_1 is H and CH_3;

each independent Y is H^+ or a cation; and

n is 0, 1, 2, 3, or 4.

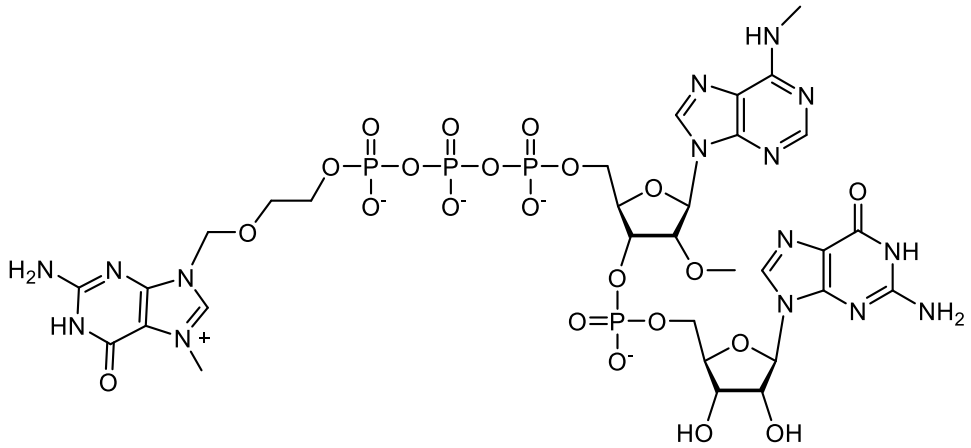
52. The compound of claim 51, wherein the compound has the following structure:



Compound 82

or a stereoisomer thereof.

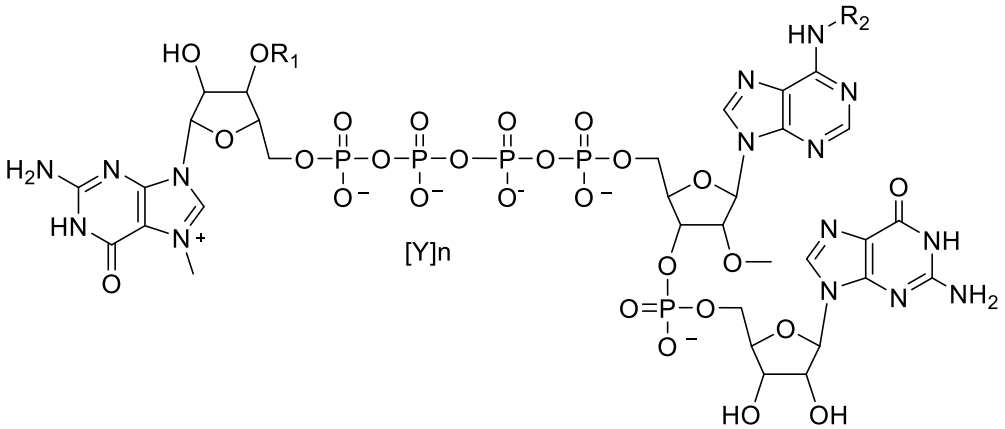
53. The compound of claim 51, wherein the compound has the following structure:



Compound 78

or a stereoisomer thereof.

54. A compound of the following formula:



Formula XII

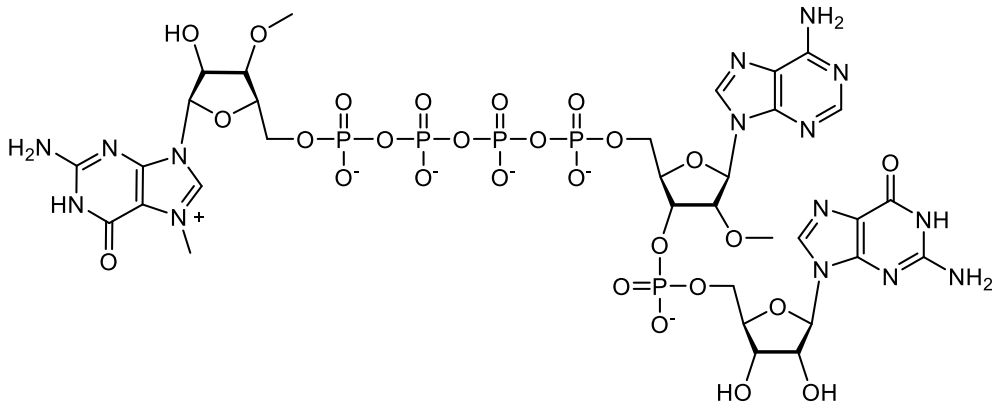
or a stereoisomer thereof, wherein:

R_1 and R_2 are each independently selected from H and CH_3;

each independent Y is H^+ or a cation; and

n is 0, 1, 2, 3, 4, or 5.

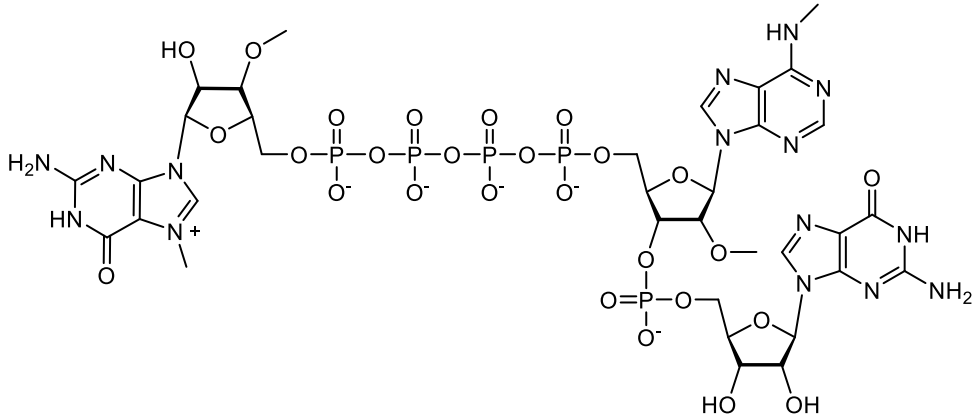
55. The compound of claim 54, wherein the compound has the following structure:



Compound 79

or a stereoisomer thereof.

56. The compound of claim 54, wherein the compound has the following structure:

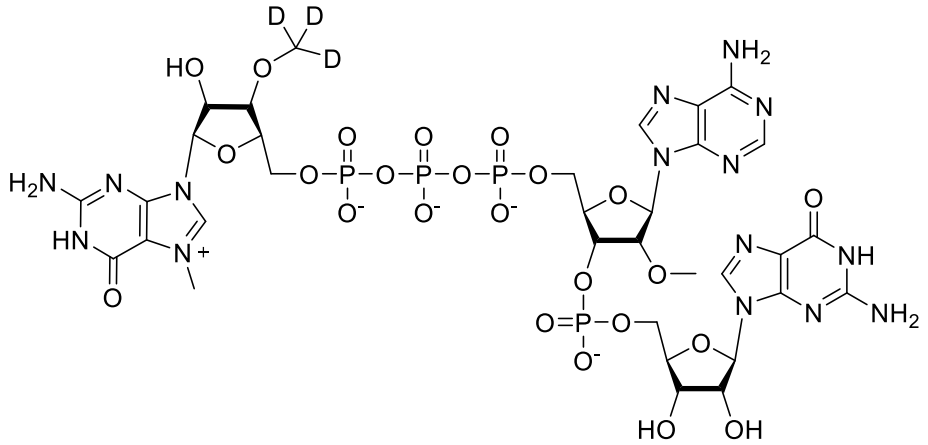


Compound 80

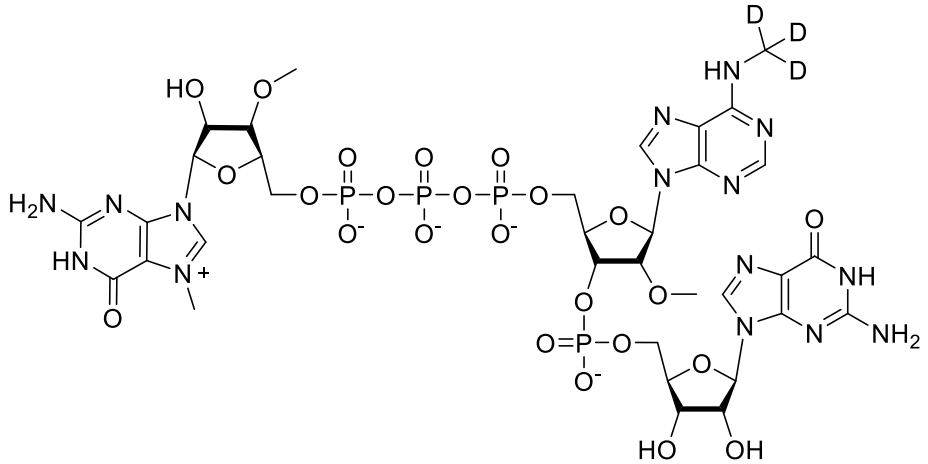
or a stereoisomer thereof.

57. The compound of any one of claims 1-56, wherein the compound is a deuterated form of the compound.

58. A compound selected from the group consisting of:



Compound 83



Compound 84

or a stereoisomer thereof.

59. A pharmaceutical composition, comprising a compound of any one of claims 1-58 and a pharmaceutically acceptable carrier.

60. An RNA molecule comprising a 5’-cap, wherein the 5’-cap comprises a compound of any one of claims 1-58.

61. The RNA molecule of claim 60, wherein the RNA molecule is a messenger RNA (mRNA) molecule or a self-amplifying RNA (saRNA) molecule

62. A method of inducing a therapeutic effect in a subject, comprising administering to the subject an RNA molecule according to claim 60 or 61.

63. A method of administering to an animal a therapeutic dose unit of an mRNA molecule comprising a 5’-cap, wherein the 5’-cap comprises a compound of any one of claims 1-58.

64. The method of claim 63, wherein the therapeutic dose unit of the mRNA molecule comprises less than 7 ng/µg of double stranded RNA (dsRNA).

65. The method of claim 64, wherein the subject exhibits increased tolerability to the administered therapeutic dose unit of the mRNA molecule as compared to an equivalent therapeutic dose unit of the mRNA molecule comprising 7 ng/µg or greater dsRNA.

66. The method of claim 65, wherein the increased tolerability is determined by measuring one or more of body weight, organ weight, aspartate aminotransferase (AST) levels, alanine transaminase (ALT) levels, C-reactive protein (CRP) levels, procalcitonin (PCT) levels, interleukin-6 (IL-6) levels, erythrocyte sedimentation rate (ESR), serum amyloid A levels, and serum ferritin levels prior to the administering and a period of time after the administering.

67. The method of claim 65 or 66, wherein the increased tolerability is measured by testing in a standard *in vivo* assay.

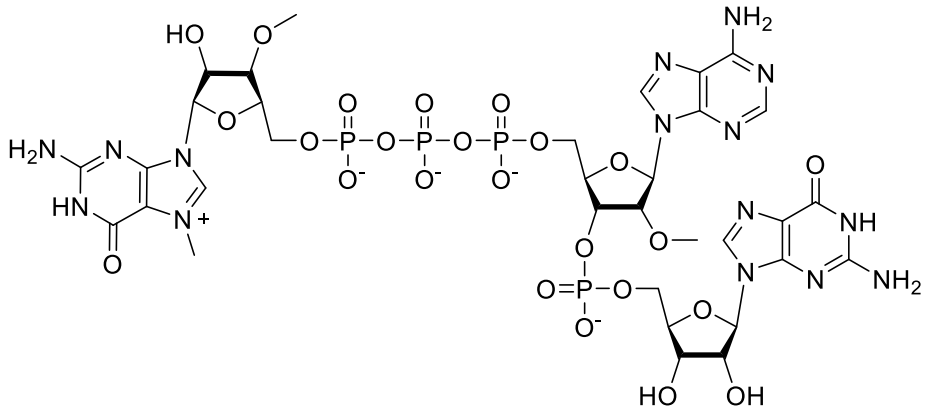
68. The method of any one of claims 65-67, wherein the increased tolerability is an increase in tolerability of at least 20 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 25 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 30 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 35 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 40 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 45 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 50 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 55 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 60 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 65 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 70 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 75 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 80 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 85 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 90 % to the administered dose unit as measured by testing in a standard *in vivo* assay, or at least 95 % to the administered dose unit as measured by testing in a standard *in vivo* assay.

69. The method of any one of claims 65-68, wherein the therapeutic dose unit of the mRNA molecule comprises less than 6.9 ng/µg of double stranded RNA (dsRNA), less than

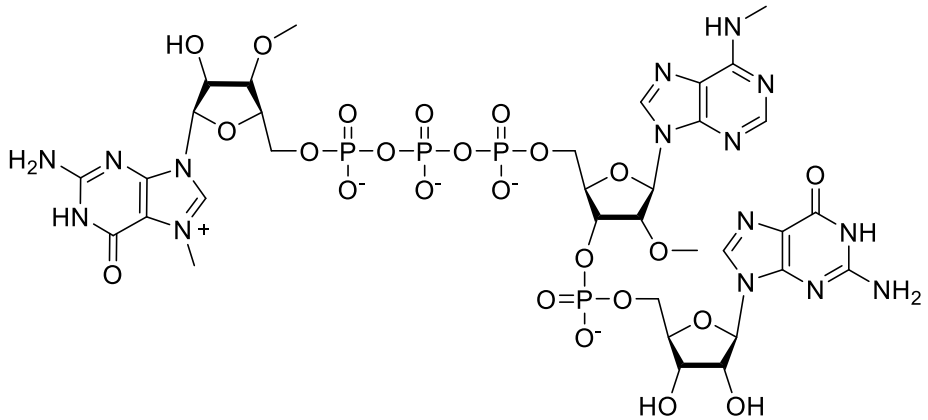
6.8 ng/µg of double stranded RNA (dsRNA), less than 6.7 ng/µg of double stranded RNA (dsRNA), less than 6.6 ng/µg of double stranded RNA (dsRNA), less than 6.5 ng/µg of double stranded RNA (dsRNA), less than 6.4 ng/µg of double stranded RNA (dsRNA), less than 6.3 ng/µg of double stranded RNA (dsRNA), less than 6.2 ng/µg of double stranded RNA (dsRNA), less than 6.1 ng/µg of double stranded RNA (dsRNA), less than 6.0 ng/µg of double stranded RNA (dsRNA), less than 5.9 ng/µg of double stranded RNA (dsRNA), less than 5.8 ng/µg of double stranded RNA (dsRNA), less than 5.7 ng/µg of double stranded RNA (dsRNA), less than 5.6 ng/µg of double stranded RNA (dsRNA), less than 5.5 ng/µg of double stranded RNA (dsRNA), less than 5.4 ng/µg of double stranded RNA (dsRNA), less than 5.3 ng/µg of double stranded RNA (dsRNA), less than 5.2 ng/µg of double stranded RNA (dsRNA), less than 5.1 ng/µg of double stranded RNA (dsRNA), less than 5.0 ng/µg of double stranded RNA (dsRNA), less than 4.9 ng/µg of double stranded RNA (dsRNA), less than 4.8 ng/µg of double stranded RNA (dsRNA), less than 4.7 ng/µg of double stranded RNA (dsRNA), less than 4.6 ng/µg of double stranded RNA (dsRNA), less than 4.5 ng/µg of double stranded RNA (dsRNA), less than 4.4 ng/µg of double stranded RNA (dsRNA), less than 4.3 ng/µg of double stranded RNA (dsRNA), less than 4.2 ng/µg of double stranded RNA (dsRNA), less than 4.1 ng/µg of double stranded RNA (dsRNA), less than 4.0 ng/µg of double stranded RNA (dsRNA), less than 3.9 ng/µg of double stranded RNA (dsRNA), less than 3.8 ng/µg of double stranded RNA (dsRNA), less than 3.7 ng/µg of double stranded RNA (dsRNA), less than 3.6 ng/µg of double stranded RNA (dsRNA), less than 3.5 ng/µg of double stranded RNA (dsRNA), less than 3.4 ng/µg of double stranded RNA (dsRNA), less than 3.3 ng/µg of double stranded RNA (dsRNA), less than 3.2 ng/µg of double stranded RNA (dsRNA), less than 3.1 ng/µg of double stranded RNA (dsRNA), less than 3.0 ng/µg of double stranded RNA (dsRNA), less than 2.9 ng/µg of double stranded RNA (dsRNA), less than 2.8 ng/µg of double stranded RNA (dsRNA), less than 2.7 ng/µg of double stranded RNA (dsRNA), less than 2.6 ng/µg of double stranded RNA (dsRNA), less than 2.5 ng/µg of double stranded RNA (dsRNA), less than 2.4 ng/µg of double stranded RNA (dsRNA), less than 2.3 ng/µg of double stranded RNA (dsRNA), less than 2.2 ng/µg of double stranded RNA (dsRNA), less than 2.1 ng/µg of double stranded RNA (dsRNA), less than 2.0 ng/µg of double stranded RNA (dsRNA), less than 1.9 ng/µg of double stranded RNA (dsRNA), less than 1.8 ng/µg of double stranded RNA (dsRNA), less than 1.7 ng/µg of double stranded RNA (dsRNA), less than 1.6 ng/µg of double stranded RNA (dsRNA), less than 1.5 ng/µg of double stranded RNA (dsRNA), less than 1.4 ng/µg of double stranded RNA (dsRNA), less than 1.3 ng/µg of double stranded RNA (dsRNA), less than 1.2 ng/µg of double stranded

RNA (dsRNA), less than 1.1 ng/µg of double stranded RNA (dsRNA), less than 1.0 ng/µg of double stranded RNA (dsRNA), less than 0.9 ng/µg of double stranded RNA (dsRNA), less than 0.8 ng/µg of double stranded RNA (dsRNA), less than 0.7 ng/µg of double stranded RNA (dsRNA), less than 0.6 ng/µg of double stranded RNA (dsRNA), less than 0.5 ng/µg of double stranded RNA (dsRNA), less than 0.4 ng/µg of double stranded RNA (dsRNA), less than 0.3 ng/µg of double stranded RNA (dsRNA), less than 0.2 ng/µg of double stranded RNA (dsRNA), or less than 0.1 ng/µg of double stranded RNA (dsRNA).

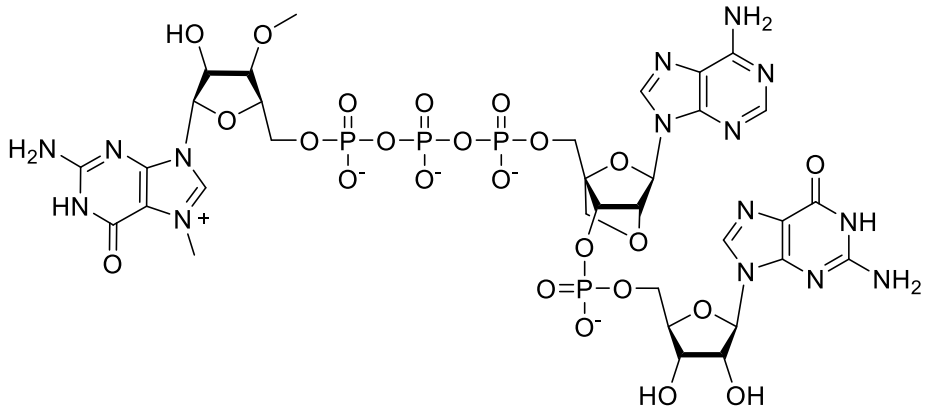
70. A method of administering to an animal a therapeutic dose unit of an mRNA molecule comprising a 5'-cap, wherein the 5'-cap comprises a compound selected from the group consisting of:



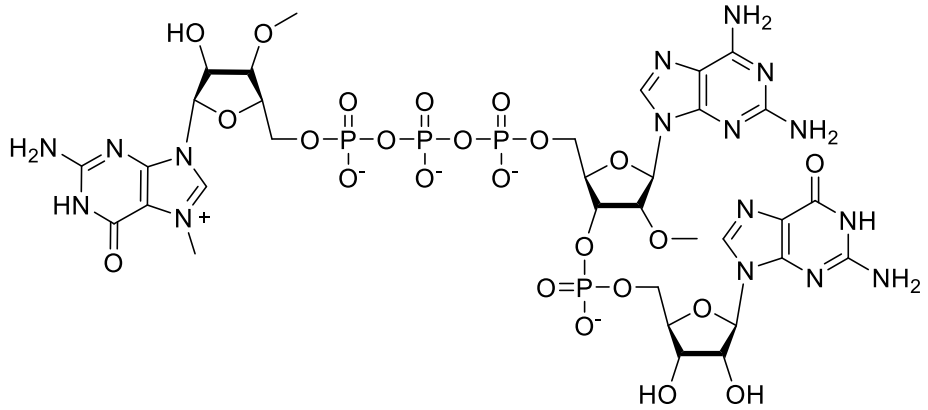
Compound 29



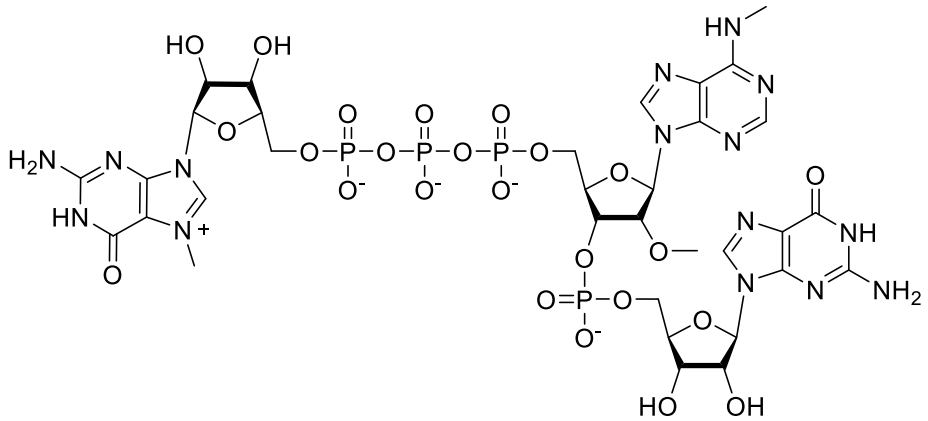
Compound 30



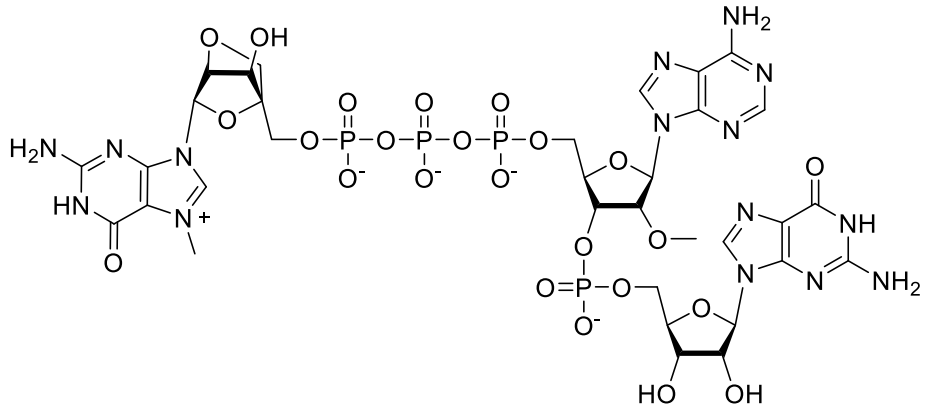
Compound 2



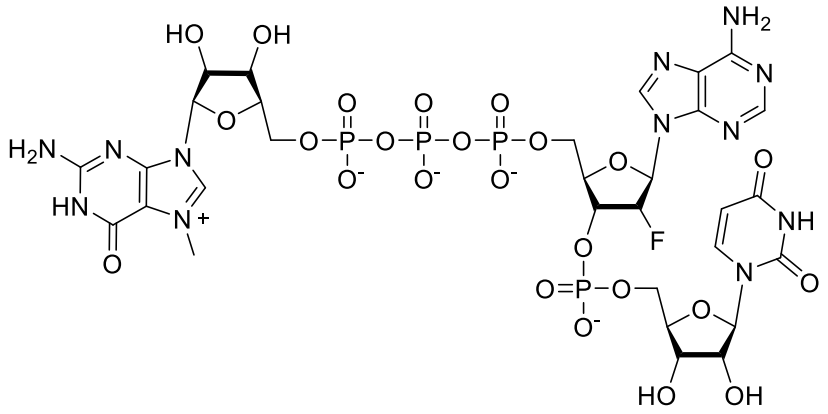
Compound 8



Compound 31



Compound 32



Compound 33

or a stereoisomer thereof,

wherein the therapeutic dose unit of the mRNA molecule comprises less than 7 ng/µg of double stranded RNA (dsRNA),

wherein the subject exhibits increased tolerability to the administered therapeutic dose unit of the mRNA molecule as compared to an equivalent therapeutic dose unit of the mRNA molecule comprising 7 ng/µg or greater dsRNA.

71. The method of claim 70, wherein the increased tolerability is determined by measuring one or more of body weight, organ weight, aspartate aminotransferase (AST) levels, alanine transaminase (ALT) levels, C-reactive protein (CRP) levels, procalcitonin (PCT) levels, interleukin-6 (IL-6) levels, erythrocyte sedimentation rate (ESR), serum amyloid A levels, and serum ferritin levels prior to the administering and a period of time after the administering.

72. The method of claim 70 or 71, wherein the increased tolerability is measured by testing in a standard *in vivo* assay.

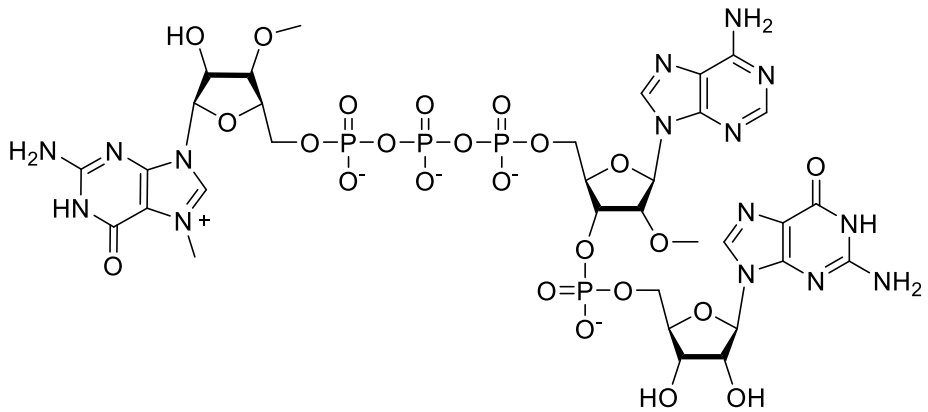
73. The method of any one of claims 70-72, wherein the increased tolerability is an increase in tolerability of at least 20 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 25 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 30 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 35 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 40 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 45 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 50 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 55 % to the administered dose unit as measured by testing in

a standard *in vivo* assay, at least 60 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 65 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 70 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 75 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 80 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 85 % to the administered dose unit as measured by testing in a standard *in vivo* assay, at least 90 % to the administered dose unit as measured by testing in a standard *in vivo* assay, or at least 95 % to the administered dose unit as measured by testing in a standard *in vivo* assay.

74. The method of any one of claims 70-73, wherein the therapeutic dose unit of the mRNA molecule comprises less than 6.9 ng/µg of double stranded RNA (dsRNA), less than 6.8 ng/µg of double stranded RNA (dsRNA), less than 6.7 ng/µg of double stranded RNA (dsRNA), less than 6.6 ng/µg of double stranded RNA (dsRNA), less than 6.5 ng/µg of double stranded RNA (dsRNA), less than 6.4 ng/µg of double stranded RNA (dsRNA), less than 6.3 ng/µg of double stranded RNA (dsRNA), less than 6.2 ng/µg of double stranded RNA (dsRNA), less than 6.1 ng/µg of double stranded RNA (dsRNA), less than 6.0 ng/µg of double stranded RNA (dsRNA), less than 5.9 ng/µg of double stranded RNA (dsRNA), less than 5.8 ng/µg of double stranded RNA (dsRNA), less than 5.7 ng/µg of double stranded RNA (dsRNA), less than 5.6 ng/µg of double stranded RNA (dsRNA), less than 5.5 ng/µg of double stranded RNA (dsRNA), less than 5.4 ng/µg of double stranded RNA (dsRNA), less than 5.3 ng/µg of double stranded RNA (dsRNA), less than 5.2 ng/µg of double stranded RNA (dsRNA), less than 5.1 ng/µg of double stranded RNA (dsRNA), less than 5.0 ng/µg of double stranded RNA (dsRNA), less than 4.9 ng/µg of double stranded RNA (dsRNA), less than 4.8 ng/µg of double stranded RNA (dsRNA), less than 4.7 ng/µg of double stranded RNA (dsRNA), less than 4.6 ng/µg of double stranded RNA (dsRNA), less than 4.5 ng/µg of double stranded RNA (dsRNA), less than 4.4 ng/µg of double stranded RNA (dsRNA), less than 4.3 ng/µg of double stranded RNA (dsRNA), less than 4.2 ng/µg of double stranded RNA (dsRNA), less than 4.1 ng/µg of double stranded RNA (dsRNA), less than 4.0 ng/µg of double stranded RNA (dsRNA), less than 3.9 ng/µg of double stranded RNA (dsRNA), less than 3.8 ng/µg of double stranded RNA (dsRNA), less than 3.7 ng/µg of double stranded RNA (dsRNA), less than 3.6 ng/µg of double stranded RNA (dsRNA), less than 3.5 ng/µg of double stranded RNA (dsRNA), less than 3.4 ng/µg of double stranded RNA (dsRNA), less than 3.3 ng/µg of double stranded RNA (dsRNA), less than 3.2 ng/µg of double stranded

RNA (dsRNA), less than 3.1 ng/µg of double stranded RNA (dsRNA), less than 3.0 ng/µg of double stranded RNA (dsRNA), less than 2.9 ng/µg of double stranded RNA (dsRNA), less than 2.8 ng/µg of double stranded RNA (dsRNA), less than 2.7 ng/µg of double stranded RNA (dsRNA), less than 2.6 ng/µg of double stranded RNA (dsRNA), less than 2.5 ng/µg of double stranded RNA (dsRNA), less than 2.4 ng/µg of double stranded RNA (dsRNA), less than 2.3 ng/µg of double stranded RNA (dsRNA), less than 2.2 ng/µg of double stranded RNA (dsRNA), less than 2.1 ng/µg of double stranded RNA (dsRNA), less than 2.0 ng/µg of double stranded RNA (dsRNA), less than 1.9 ng/µg of double stranded RNA (dsRNA), less than 1.8 ng/µg of double stranded RNA (dsRNA), less than 1.7 ng/µg of double stranded RNA (dsRNA), less than 1.6 ng/µg of double stranded RNA (dsRNA), less than 1.5 ng/µg of double stranded RNA (dsRNA), less than 1.4 ng/µg of double stranded RNA (dsRNA), less than 1.3 ng/µg of double stranded RNA (dsRNA), less than 1.2 ng/µg of double stranded RNA (dsRNA), less than 1.1 ng/µg of double stranded RNA (dsRNA), less than 1.0 ng/µg of double stranded RNA (dsRNA), less than 0.9 ng/µg of double stranded RNA (dsRNA), less than 0.8 ng/µg of double stranded RNA (dsRNA), less than 0.7 ng/µg of double stranded RNA (dsRNA), less than 0.6 ng/µg of double stranded RNA (dsRNA), less than 0.5 ng/µg of double stranded RNA (dsRNA), less than 0.4 ng/µg of double stranded RNA (dsRNA), less than 0.3 ng/µg of double stranded RNA (dsRNA), less than 0.2 ng/µg of double stranded RNA (dsRNA), or less than 0.1 ng/µg of double stranded RNA (dsRNA).

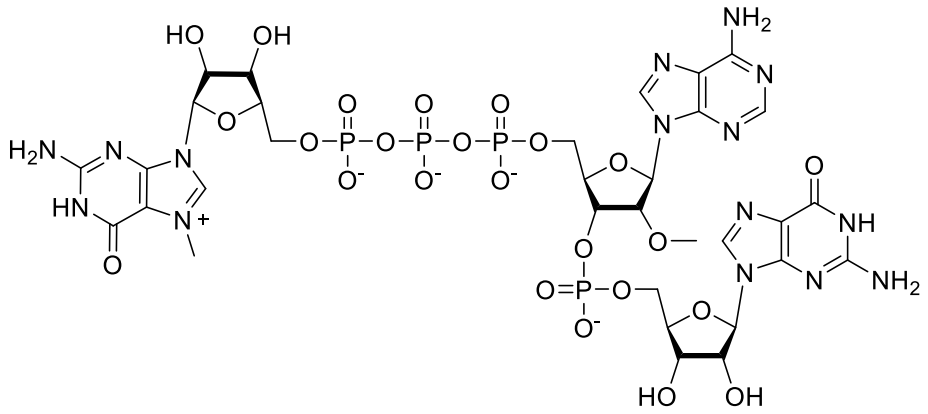
75. A method for increasing *in vivo* translation of a polypeptide in a subject, comprising administering to the subject a therapeutic dose unit comprising an effective amount of an mRNA encoding a polypeptide, wherein the mRNA comprises a 5’-cap having the following formula:



Compound 29

or a stereoisomer thereof,

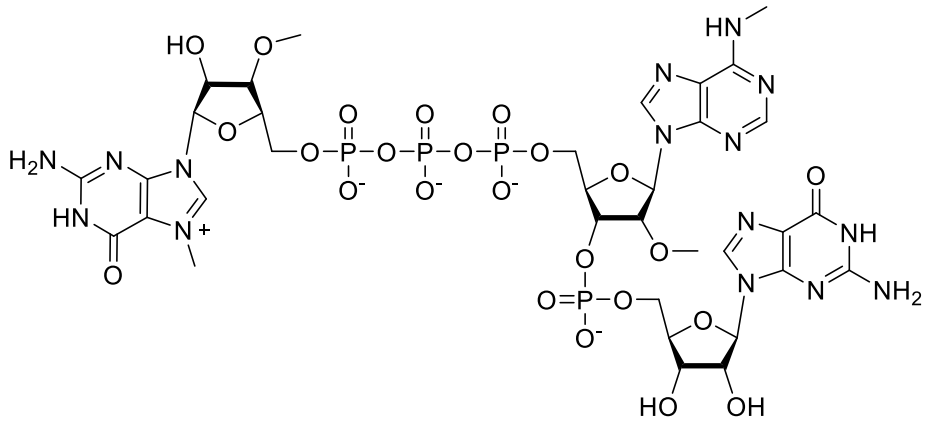
wherein the administered therapeutic dose unit is at least 20 % lower than the therapeutic dose unit required to elicit the same response in the subject when administered a comparative mRNA encoding the polypeptide, wherein the comparative mRNA comprises a 5'-cap having the following formula:



^{m7}GpppA$_{2'OMe}$pG ("Control")

or a stereoisomer thereof.

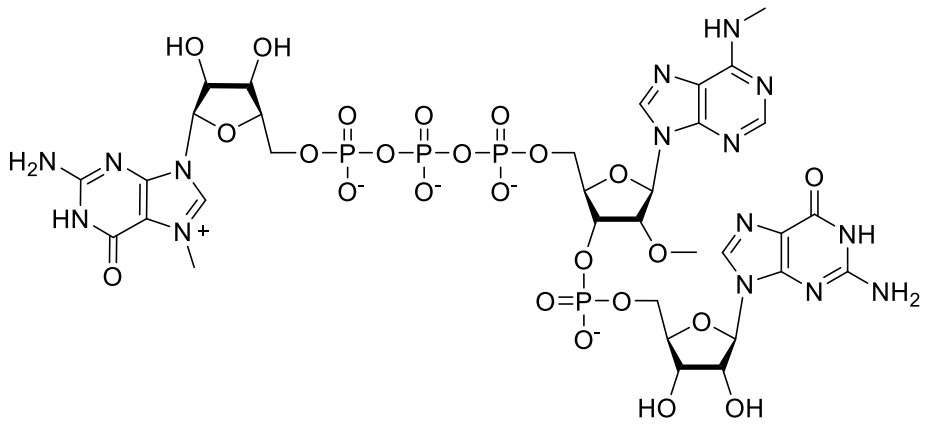
76. A method for increasing *in vivo* translation of a polypeptide in a subject, comprising administering to the subject a therapeutic dose unit comprising an effective amount of an mRNA encoding a polypeptide, wherein the mRNA comprises a 5'-cap having the following formula:



Compound 30

or a stereoisomer thereof,

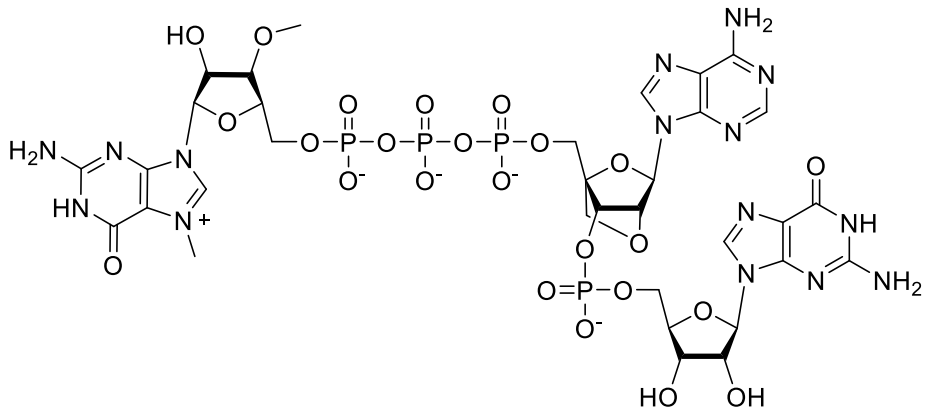
wherein the administered therapeutic dose unit is at least 20 % lower than the therapeutic dose unit required to elicit the same response in the subject when administered a comparative mRNA encoding the polypeptide, wherein the comparative mRNA comprises a 5'-cap having the following formula:



Compound 31

or a stereoisomer thereof.

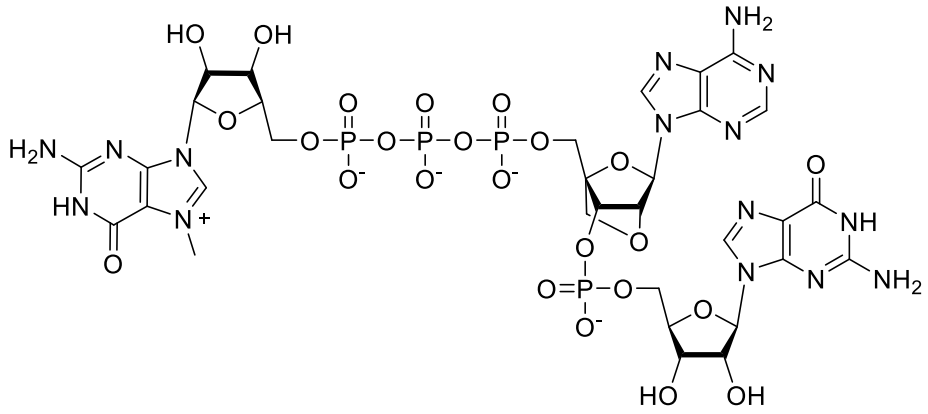
77. A method for increasing *in vivo* translation of a polypeptide in a subject, comprising administering to the subject a therapeutic dose unit comprising an effective amount of an mRNA encoding a polypeptide, wherein the mRNA comprises a 5'-cap having the following formula:



Compound 2

or a stereoisomer thereof,

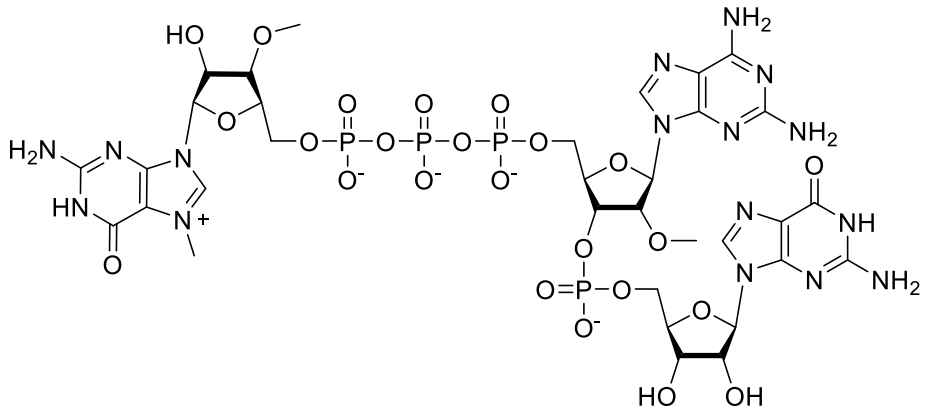
wherein the administered dose is at least 20 % lower than the therapeutic dose unit required to elicit the same response in the subject when administered a comparative mRNA encoding the polypeptide, wherein the comparative mRNA comprises a 5'-cap having the following formula:



Compound 1

or a stereoisomer thereof.

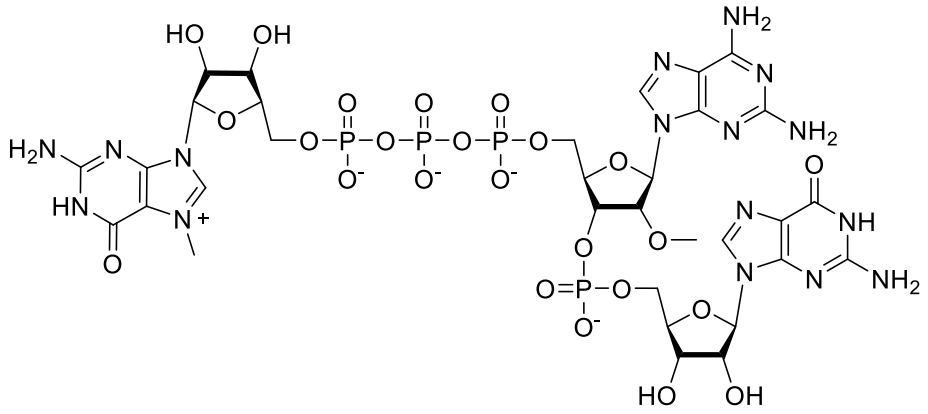
78. A method for increasing *in vivo* translation of a polypeptide in a subject, comprising administering to the subject a therapeutic dose unit comprising an effective amount of an mRNA encoding a polypeptide, wherein the mRNA comprises a 5'-cap having the following formula:



Compound 8

or a stereoisomer thereof,

wherein the administered therapeutic dose unit is at least 20 % lower than the therapeutic dose unit required to elicit the same response in the subject when administered a comparative mRNA encoding the polypeptide, wherein the comparative mRNA comprises a 5'-cap having the following formula:



Compound 7

or a stereoisomer thereof.

79. The method of claim 75-78, wherein the subject exhibits increased tolerability to the administered therapeutic dose unit as compared to the therapeutic dose unit required to elicit the same response in the subject when administered the comparative mRNA, as measured by testing in a standard *in vivo* assay.

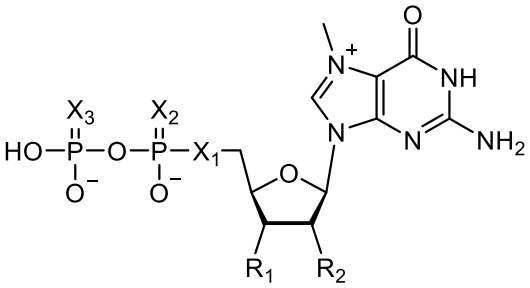
80. The method of claim 79, wherein the increased tolerability is an increase in tolerability of at least 20 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 25 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 30 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 35 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 40 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 45 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 50 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 55 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 60 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 65 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 70 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 75 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 80 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 85 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, at least 90 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay, or at least 95 % to the administered therapeutic dose unit as measured by testing in a standard *in vivo* assay.

81. The method of any one of claims 75-80, wherein the administered therapeutic dose unit comprises less than 6.9 ng/µg of double stranded RNA (dsRNA), less than 6.8 ng/µg of double stranded RNA (dsRNA), less than 6.7 ng/µg of double stranded RNA (dsRNA), less than 6.6 ng/µg of double stranded RNA (dsRNA), less than 6.5 ng/µg of double stranded RNA (dsRNA), less than 6.4 ng/µg of double stranded RNA (dsRNA), less than 6.3 ng/µg of double stranded RNA (dsRNA), less than 6.2 ng/µg of double stranded RNA (dsRNA), less than 6.1 ng/µg of double stranded RNA (dsRNA), less than 6.0 ng/µg of double stranded RNA (dsRNA), less than 5.9 ng/µg of double stranded RNA (dsRNA), less than 5.8 ng/µg of double stranded RNA (dsRNA), less than 5.7 ng/µg of double stranded RNA (dsRNA), less than 5.6 ng/µg of double stranded RNA (dsRNA), less than 5.5 ng/µg of double stranded RNA (dsRNA), less than 5.4 ng/µg of double stranded RNA (dsRNA), less than 5.3 ng/µg of double stranded RNA (dsRNA), less than 5.2 ng/µg of double stranded RNA (dsRNA), less than 5.1 ng/µg of double stranded RNA (dsRNA), less than 5.0 ng/µg of double stranded RNA (dsRNA), less than 4.9 ng/µg of double stranded RNA (dsRNA), less than 4.8 ng/µg of double stranded RNA (dsRNA), less than 4.7 ng/µg of double stranded RNA (dsRNA), less than 4.6 ng/µg of double stranded RNA (dsRNA), less than 4.5 ng/µg of double stranded RNA (dsRNA), less than 4.4 ng/µg of double stranded RNA (dsRNA), less than 4.3 ng/µg of double stranded RNA (dsRNA), less than 4.2 ng/µg of double stranded RNA (dsRNA), less than 4.1 ng/µg of double stranded RNA (dsRNA), less than 4.0 ng/µg of double stranded RNA (dsRNA), less than 3.9 ng/µg of double stranded RNA (dsRNA), less than 3.8 ng/µg of double stranded RNA (dsRNA), less than 3.7 ng/µg of double stranded RNA (dsRNA), less than 3.6 ng/µg of double stranded RNA (dsRNA), less than 3.5 ng/µg of double stranded RNA (dsRNA), less than 3.4 ng/µg of double stranded RNA (dsRNA), less than 3.3 ng/µg of double stranded RNA (dsRNA), less than 3.2 ng/µg of double stranded RNA (dsRNA), less than 3.1 ng/µg of double stranded RNA (dsRNA), less than 3.0 ng/µg of double stranded RNA (dsRNA), less than 2.9 ng/µg of double stranded RNA (dsRNA), less than 2.8 ng/µg of double stranded RNA (dsRNA), less than 2.7 ng/µg of double stranded RNA (dsRNA), less than 2.6 ng/µg of double stranded RNA (dsRNA), less than 2.5 ng/µg of double stranded RNA (dsRNA), less than 2.4 ng/µg of double stranded RNA (dsRNA), less than 2.3 ng/µg of double stranded RNA (dsRNA), less than 2.2 ng/µg of double stranded RNA (dsRNA), less than 2.1 ng/µg of double stranded RNA (dsRNA), less than 2.0 ng/µg of double stranded RNA (dsRNA), less than 1.9 ng/µg of double stranded RNA (dsRNA), less than 1.8 ng/µg of double stranded RNA (dsRNA), less than 1.7 ng/µg of double stranded RNA (dsRNA), less than 1.6 ng/µg of double stranded RNA (dsRNA), less than 1.5 ng/µg of double stranded

RNA (dsRNA), less than 1.4 ng/µg of double stranded RNA (dsRNA), less than 1.3 ng/µg of double stranded RNA (dsRNA), less than 1.2 ng/µg of double stranded RNA (dsRNA), less than 1.1 ng/µg of double stranded RNA (dsRNA), less than 1.0 ng/µg of double stranded RNA (dsRNA), less than 0.9 ng/µg of double stranded RNA (dsRNA), less than 0.8 ng/µg of double stranded RNA (dsRNA), less than 0.7 ng/µg of double stranded RNA (dsRNA), less than 0.6 ng/µg of double stranded RNA (dsRNA), less than 0.5 ng/µg of double stranded RNA (dsRNA), less than 0.4 ng/µg of double stranded RNA (dsRNA), less than 0.3 ng/µg of double stranded RNA (dsRNA), less than 0.2 ng/µg of double stranded RNA (dsRNA), or less than 0.1 ng/µg of double stranded RNA (dsRNA).

82. A method of synthesizing a trinucleotide compound, comprising:

(1) mixing an N7-methyl-guanosine-5'-diphosphate of the following structure:



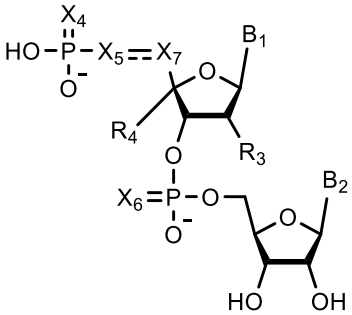
, wherein

X_1 and X_2 are each independently selected from the group consisting of O and S;

X_3 is O;

R_1 and R_2 are each independently selected from H, OH, N_3, F, substituted or unsubstituted alkoxy, and thio, wherein R_1 and R_2 optionally combine to form a heterocycle, with an activating reagent and an imidazole to form an activated intermediate; and

(2) adding a salt reagent and a dinucleotide of the following structure:



, wherein

X_4 and X_6 are each independently selected from the group consisting of O and S;

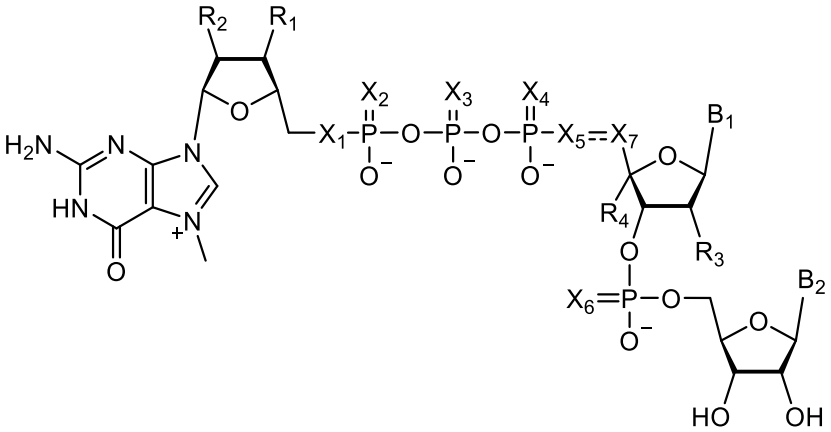
X_5 is O, S, or CH;

X_7 is CH or CH_2;

R_3 is OH, OMe, F and R_4 is H, or wherein R_3 and R_4 are covalently bonded together and, together with intermediate atoms, form a 2'-O, 4'-C methylene bridge; and

B_1 and B_2 are each independently selected from the group consisting of a purine ring and a pyrimidine ring

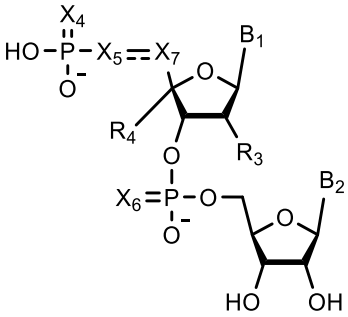
to the activated intermediate to form the trinucleotide compound of the following structure:



wherein the method is a one-pot synthesis.

83. A method of synthesizing a trinucleotide compound, comprising:

(1) mixing a dinucleotide of the following structure:



, wherein

$\equiv$ is a single bond or a double bond;

X_4 is O;

X_6 is O or S;

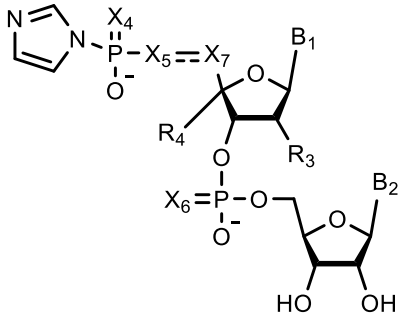
X_5 is O, S, or CH;

X_7 is CH or CH_2;

R_3 is OH, OMe, F and R_4 is H, or wherein R_3 and R_4 are covalently bonded together and, together with intermediate atoms, form a 2'-O, 4'-C methylene bridge; and

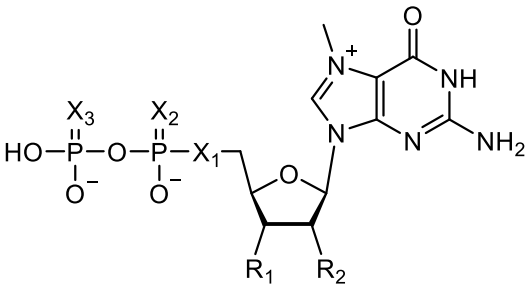
B_1 and B_2 are each independently selected from the group consisting of a purine ring and a pyrimidine ring,

with an activating reagent and an imidazole to form an activated phosphate imidazolide of the following structure:



; and

(2) adding a salt reagent and a compound of the following structure:

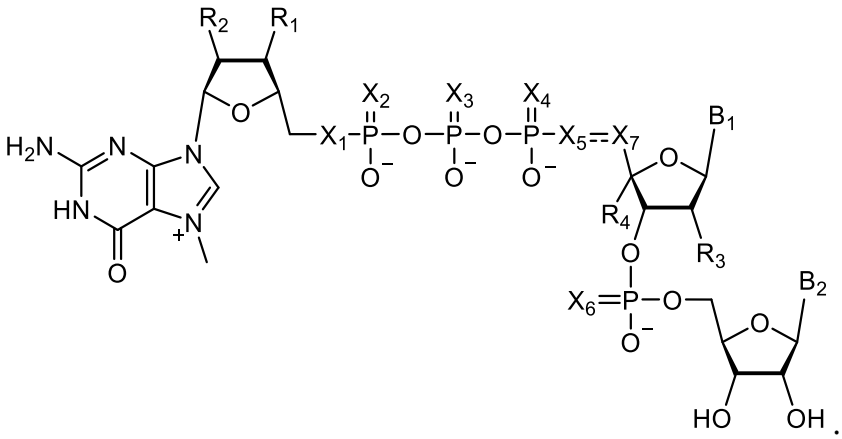


, wherein

X_1 and X_2 are each independently selected from the group consisting of O and S;

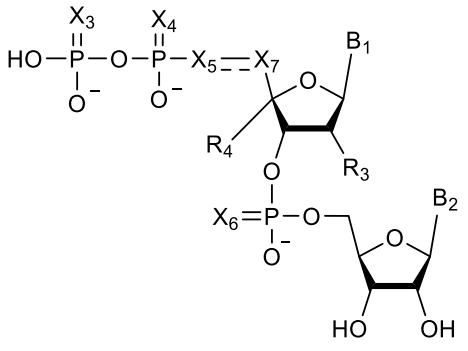
X_3 is S;

R_1 and R_2 are each independently selected from H, OH, N_3, F, substituted or unsubstituted alkoxy, and thio, wherein R_1 and R_2 optionally combine to form a heterocycle, to the activated phosphate imidazolide to form the trinucleotide compound of the following structure:



84. A method of synthesizing a trinucleotide compound, comprising:

(1) mixing a diphosphate dinucleotide of the following structure:


, wherein

--- is a single bond or a double bond;

X_3 is O;

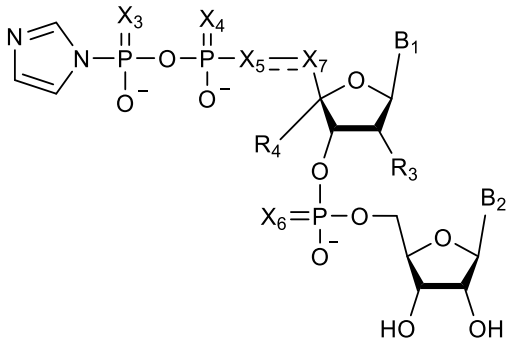
X_4 and X_6 are each independently selected from O and S;

X_5 is O, S, or CH; X_7 is CH or CH_2;

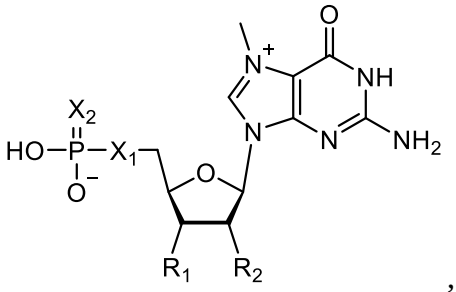
R_3 is OH, OMe, F and R_4 is H, or wherein R_3 and R_4 are covalently bonded together and, together with intermediate atoms, form a 2'-O, 4'-C methylene bridge; and

B_1 and B_2 are each independently selected from the group consisting of a purine ring and a pyrimidine ring,

with an activating reagent and an imidazole to form an activated phosphate imidazolide of the following structure:


; and

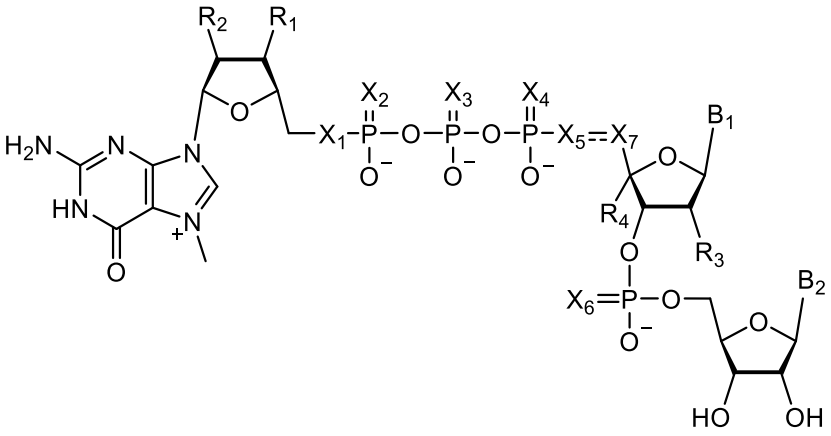
(2) adding a salt reagent and a compound of the following structure:


, wherein

X_1 and X_2 are each independently selected from O and S; and

R_1 and R_2 are each independently selected from H, OH, N_3, F, substituted or unsubstituted alkoxy, and thio, wherein R_1 and R_2 optionally combine to form a heterocycle,

to the activated phosphate imidazolide to form the trinucleotide compound of the following structure:



wherein the method is a one-pot synthesis.